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STUDIES IN DISEASES OF MUSCLE

XII. HEREDITY OF PROGRESSIVE MUSCULAR DYSTROPHY; RELATIONSHIP BETWEEN AGE AT ONSET OF SYMPTOMS AND CLINICAL COURSE

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AND
H. G. WOLFF, M.D.
NEW YORK

Progressive muscular dystrophy is generally regarded as a "hereditary disease" because patients with this condition frequently give a history of other members of the family who have been similarly affected. Numerous families have been reported in which the disease has appeared in different generations, but the genealogic studies thus far have been too few and incomplete. In consequence, the mechanism of the hereditary transmission of progressive muscular dystrophy is still imperfectly understood. The difficulties usually encountered in obtaining data on heredity in human beings are considerably increased in the case of progressive muscular dystrophy. Unlike conditions, such as hemophilia and color blindness, which can always be demonstrated early in life in affected persons and of which the mode of hereditary transmission is well understood, progressive muscular dystrophy need not manifest itself until later in life. Therefore, members of the family who are without symptoms cannot be considered free from the disease until they have passed an age at which the development of the disease would appear improbable. Moreover, patients in whom symptoms of progressive muscular dystrophy develop before the third decade usually have no descendants.

In the present state of knowledge, the publication of factual information is important. The elucidation of the problem will be possible only when a sufficient number of "dystrophy families" have been followed through several generations, or when large numbers of less complete family trees have been studied. It is for this reason that the present data are reported.

MATERIAL AND METHODS

During the past twelve years a large number of patients with progressive muscular dystrophy were examined. For 86 of these all available information regarding the hereditary transmission of the disease was obtained. These patients were members of 75 different families, in which 39 additional members were affected with the disease—a total of 125 persons on whom data regarding the heredity of muscular dystrophy were ascertained. In all instances in which it was possible other members of these families were examined for evidence of the disease. The importance of examining other members of affected families was emphasized on a few occasions when relatives alleged to have progressive muscular dystrophy were found instead to have some unrelated condition. Practically all of the 86 patients who were examined were followed at regular intervals over long periods. In addition, metabolic studies were made on many of these patients at frequent intervals over periods of several years. All the information available on the remaining 39 patients, who were not examined by us, was obtained. Many of these patients had been examined in other hospitals or had been seen by other physicians, and in these instances full reports were requested.

This study was aided by a grant from the National Foundation for Infantile Paralysis, Inc.

From the Departments of Medicine and Psychiatry, Cornell University Medical College; the Russell Sage Institute of Pathology, and the New York Hospital.

OBSERVATIONS AND COMMENT

Incidence of Positive Familial History.—The data are shown in the table. Of the 86 patients who were examined, 35 per cent gave a history of at least 1 other member of the family with the disease, and 54 per cent of the total series of 125 patients, which included all the affected members of the families investigated, gave a positive familial history of the disease. In 27 per cent of the 75 families investigated 2 or more members had muscular dystrophy; in each of the remaining 73 per cent of the families only 1 member was known to have had the disease.

These observations agree, on the whole, with those of other investigators. In only 14 of the 44 cases of pseudohypertrophic muscular dystrophy described by Gowers [1] did the patients come of families without muscular disease; the remaining 30 cases (68 per cent) were distributed among 10 families. Gowers found data on 176 additional cases in the literature, and of the total of 220 cases, 102 were without familial occurrence and 118 (53.6 per cent) were distributed among 39 families. Poore [2] reported 1 case and analyzed 85 cases in the literature. In 43 (50 per cent) of the total of 86 cases a positive familial history was obtained.

Data on Inheritance of Progressive Muscular Dystrophy in One Hundred and Twenty-Five Persons

Patients *	Number	Familial History		Sex Incidence		
		Positive, %	Negative, %	Males	Females	Ratio Males:Females
Examination	85	35	65	67	19	3.5:1
Data from examination and history	125	34	46	94	31	3:1
Heredity by simple sex-linked recessive factor †	26	..	..	26	0	
Heredity by dominant factor	14	..	..	7	7	1:1
Heredity of undetermined type, including "sporadic" occurrence and lineal inheritance	85	..	..	61	24	2.5:1
Lineal inheritance	27	..	..	14	13	1:1

* The patients were members of 75 different families; in 73 per cent of these families there was only 1 person with the disease, and in the remaining 27 per cent at least 2 persons were affected

† The muscular dystrophy appeared in the males but was transmitted by apparently healthy females.

Familial incidence was found in 42 per cent of the 36 cases described by Hurwitz.[3] Sjövall [4] stated that of 157 cases, 63 were isolated, giving a familial incidence of 60 per cent.

Sex Incidence.—There were 67 males and 19 females in the group of 86 patients who were examined. The ratio of males to females in this group was 3.5:1. Of the total series of 125 patients, 94 were males and 31 were females, a ratio of 3:1.

The sex ratio observed in this series was similar to that in most series previously reported. Weitz,[5] in a compilation of 639 cases from the literature, found that males were affected two and nine-tenths times as often as females. These

1. Gowers, W. R.: Pseudo-Hypertrophic Muscular Paralysis: A Clinical Lecture, London, J. & A. Churchill, 1879.

2. Poore, C. T.: Pseudo-Hypertrophic Muscular Paralysis, with an Analysis of Cases, New York M. J. **21**:569, 1875.

3. Hurwitz, S.: Primary Myopathies: Report of Thirty-Six Cases and Review of the Literature, Arch. Neurol. & Psychiat. **36**:1294 (Dec.) 1936.

4. Sjövall, B.: Dystrophia musculorum progressiva: Eine Erblichkeitsmedizinische und klinische Studie, Acta psychiat. et neurol. (supp.) **10**:1, 1936.

5. Weitz, W.: Ueber die Vererbung bei der Muskeldystrophie, Deutsche Ztschr. f. Nervenh. **72**:143, 1921.

cases represented various clinical types of muscular dystrophy. In the series reported by Funsten [6] there were 25 males and 5 females. Grothaus [7] studied 30 patients with progressive muscular dystrophy in the surgical clinic at Freiburg, Germany, and, by means of church records, investigated the family trees of the patients back to 1800. The records went back 9 generations, but only those of 5 generations were used. In the series of patients examined by Grothaus the ratio of males to females was 3:1, but for the 257 persons for whom data were obtained from the family records the ratio was 1.4:1. Sjövall [4] found a ratio of males to females of 2:1 in the records of 157 patients who had been seen in several

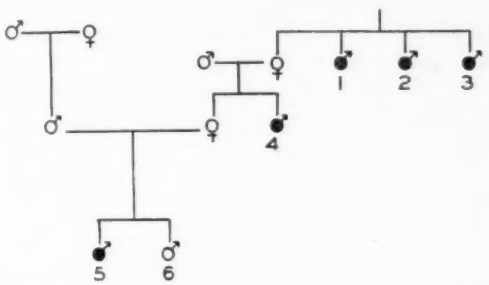

Fig. 1.—Patient *5*, aged 8 years, had a moderately advanced condition, with onset at the age of 2 years. Sibling *6*, aged 7 months, was without muscular involvement. Subjects *1*, *2*, *3* and *4* had onset of muscular symptoms in childhood and became totally incapacitated at about puberty.

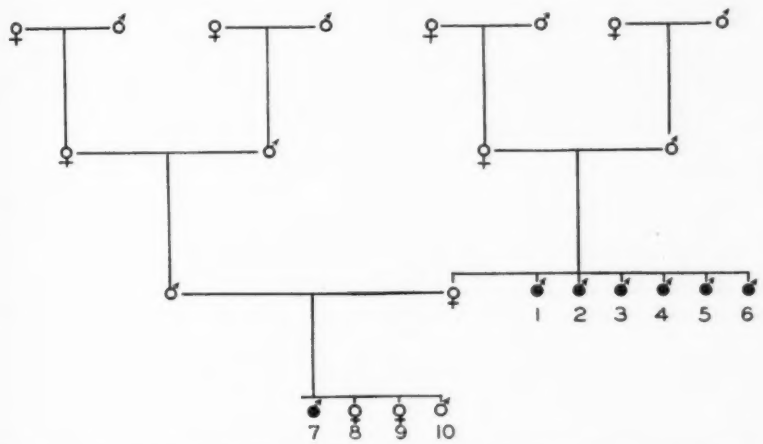

Fig. 2.—In patients *1* to *6* dystrophy developed at the age of 7 years. Patient *1* died at the age of 20, of pulmonary infection, when muscular disability was far advanced. Patients *2*, *3*, *4* and *5*, aged 23, 18, 16 and 13 years respectively, are unable to walk or stand. Patient *6*, aged 11 years, can still walk, although with difficulty. Patient *7*, aged 5½ years, first showed symptoms at the age of 2 years. His siblings, *8*, *9* and *10*, are 4½, 2½ and 1½ years old respectively.

clinics in Lund, Stockholm and Uppsala, Sweden, during the years from 1910 to 1930. The patients were members of 105 families. A considerably higher

6. Funsten; R. V.: Muscular Dystrophy, J. Bone & Joint Surg. **5**:190, 1923.

7. Grothaus, E.: Untersuchungen über den Erbgang der Dystrophia musculorum progressiva (Erb), Arch. f. klin. Chir. **181**:344, 1934.

sex ratio was reported by Hough,[8] Mettel and Slocum[9] and Voshell.[10] In each of the series of 43 and 48 patients observed by Hough and by Mettel and Slocum, respectively, there was only 1 female. Voshell reported that in his experience of about 25 cases only 2 females were seen.

However, in instances in which inheritance is by a dominant factor both sexes usually are affected with equal frequency. Thus, in this series, for the 14 patients in whom inheritance of the disease was dominant the sex ratio was 1 : 1. A similar sex ratio was seen in the family reported by Pearson.[11] Eight members in 4 generations were affected; of these, 4 were males and 4 females.

Types of Hereditary Transmission.—In 26 males in the total of 125 patients the inheritance of progressive muscular dystrophy was by a simple sex-linked recessive factor. Two of the family trees are shown in figures 1 and 2. These 26 patients were members of 5 of the total of 75 families in this series. In these 5 families males alone were affected, the gene containing the factor for muscular dystrophy

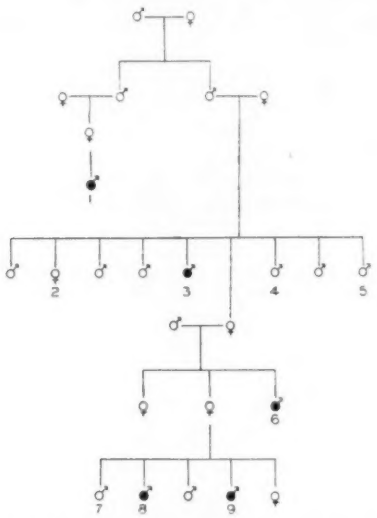

Fig. 3.—Patients *3*, *6* and *9* had muscular dystrophy, with onset at the ages of 7 to 10 years; patients *3* and *6* died at 15 years of age, of pulmonary infection; patient *9* died at the age of 14 years, after an operation for acute appendicitis. Patient *8*, aged 9 years, with moderately advanced dystrophy, first had symptoms at the age of 7 years. Subject *1* is said to have had dystrophy, but the diagnosis is not certain.

having been transmitted by apparently healthy females to their affected sons. All the mothers of these patients had male siblings with the disease. In 3 of the families every male descendant on whom data were available had muscular dystrophy. However, in 1 family (fig. 3) the disease developed in only 4 out of a total of 12 males in 3 generations. In addition to these affected members, 1 male descendant on the maternal great-grandfather's side of the family is said to have had muscular disability similar to that of our patient (*8*, fig. 3). In another family

8. Hough, G. De N.: Two Cases of Atypical Familial Dystrophy, New England J. Med. **206**:396, 1932.

9. Mettel, H. B., and Slocum, Y. K.: Pseudohypertrophic Muscular Dystrophy: Preliminary Report on the Treatment of Three Cases with Glycine, J. Pediat. **3**:352, 1933.

10. Voshell, A. F.: Progressive Pseudohypertrophic Muscular Dystrophy, South. M. J. **26**:156, 1933.

11. Pearson, K.: Two New Pedigrees of Muscular Dystrophy, Ann. Eugenics **5**:179, 1933.

4 out of a total of 9 males had muscular dystrophy (fig. 4). The latter family is of considerable interest in that the mother of our patients was twice married and had a son with dystrophy by each of the husbands. The issue of the second marriage was twins; the girl has shown no muscular symptoms, whereas dystrophy developed in the boy. The mother showed no evidence of the disease, but her brother had muscular dystrophy. An apparently healthy sister of the mother had a son who became affected with the disease. In another family 2 females of a sibling group of 4 females and 3 males had dystrophy; 1 of the apparently healthy females

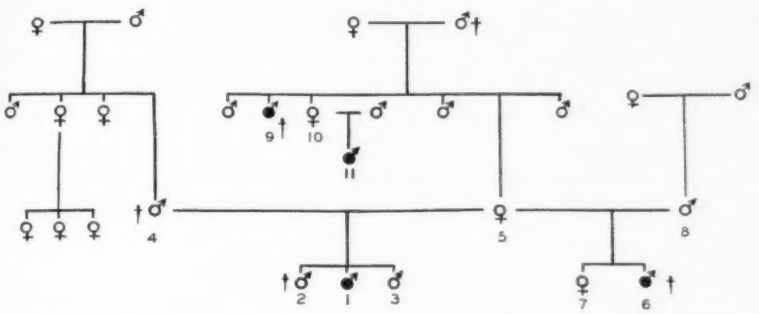

Fig. 4.—Patient *1*, aged 10 years, with pseudyhypertrophic muscular dystrophy, had onset of symptoms at the age of about 5 years. A brother (*2*) died at 3 months of age, of diarrhea. Another brother (*3*), aged 8 years, is normal. The father (*4*) was well until his death, at the age of 33, of appendicitis. The mother (*5*), aged 30, has no muscular symptoms. A stepbrother of the patient (*6*) had dystrophy and died at the age of 2 years, of pertussis; a twin sister of this child (*7*), now aged 3 years, is normal. The father of these twins (*8*) is well, at the age of 28. Subject *9* had dystrophy and died at the age of 19. Subject *10*, aged 39, is normal but has a son (*11*) with muscular dystrophy. (*1* was a patient in the children's clinic, the New York Hospital. Dr. Samuel Z. Levine gave us permission to publish these data.)

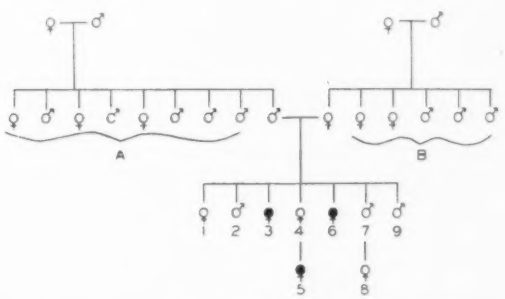

Fig. 5.—Members of groups *A* and *B* showed no evidence of muscular disease. All had several children, all of whom were normal. Subject *1* died at the age of 5 years, without muscular symptoms. Subjects *2*, *4*, *7*, *8* and *9* are well at the ages of 32, 27, 34, 1 and 30 years, respectively. Patient *3* is 18 years old and has moderately advanced muscular dystrophy. Patient *5*, aged 5 years, has had progressive muscular weakness since the age of 1 year, and has difficulty in walking. Subject *6*, aged 29, showed generalized weakness at the age of 2 years. Her muscular dystrophy is now advanced.

of this group had a daughter in whom the disease developed. In this instance heredity was by a recessive factor which was not sex linked (fig. 5).

In 14 patients inheritance of the disease can be interpreted as having been by a dominant factor. Each patient had a parent who was affected by the disease, and all descendants of healthy parents were free from all evidence of muscular dystrophy. The 14 patients were members of 2 families. In 1 family a father and

his son were affected (fig. 6); in the other family there were 6 males and 6 females with muscular disease (fig. 7). In all of these patients the disease had its onset relatively late in life. Thus, in the family illustrated in figure 6, symptoms first were noted by the father at the age of 52 and by the son at the age of 15 years. In the second family in which the muscular disease was inherited by a dominant factor the average age of the patients when symptoms first were noted was about 33 years. The muscular involvement in the affected members of this family was unusual for dystrophy in that the muscles earliest and most severely involved were those of the calves and feet. The complete data, which are presented in the next

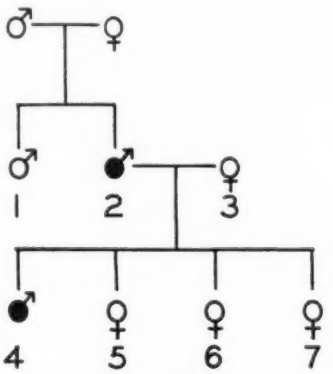

Fig. 6.—Subject *1*, aged 59 years, is strong and healthy. Patient *2*, aged 56, has wasting of the triceps muscles and the muscles of the calves and thighs; the calves are moderately enlarged; he "climbs up on himself" when straightening his body; his weakness started insidiously at the age of 52 to 53 years. In patient *4*, aged 25 years, the condition started at the age of 15 years with wasting of the thigh muscles; later the muscles of the arms and hands became wasted.

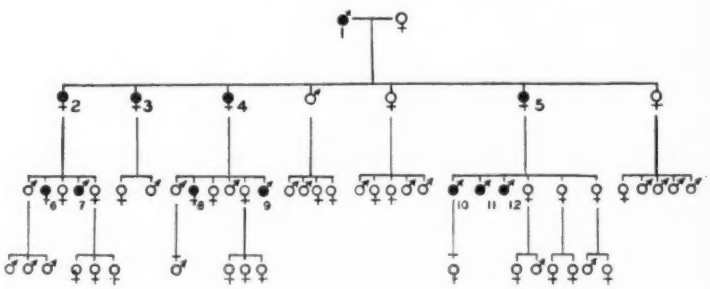

Fig. 7.—Family tree showing distal type of progressive muscular dystrophy with dominant type of heredity. Data on members of the family will be given in the next report on this series.[12]

report of this series,[12] indicate that the condition was an atrophic distal type of progressive muscular dystrophy.

Twenty-seven patients, including 14 males and 13 females, had at least 1 other sibling with dystrophy, but a history of the disease in preceding generations could not be obtained (figs. 8, 9, 10 and 11). Fifty-eight patients, of whom 47 were males and 11 females, gave a negative history for any other instance of the disease in their families.

12. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: XIII. Progressive Muscular Dystrophy of Atrophic Distal Type; Report on a Family; Report of Autopsy, Arch. Neurol. & Psychiat., this issue, p. 655.

A summary of the observations on the types of inheritance is shown in the table. For 26 patients the evidence seems conclusive that inheritance was by a simple sex-linked recessive factor, similar to that for color blindness and hemophilia. All of these patients had dystrophy of the pseudohypertrophic type, and in all, the onset of the disease was in the first decade of life. In 14 other patients inheritance was by a dominant factor (figs. 6 and 7). Leiter [13] reported on a family in which inheritance was dominant in the last 2 generations, whereas it appeared to be recessive in the preceding generation. Grothaus [7] expressed the opinion that a recessive factor can in its transmission change to a dominant one. However, the mode of inheritance in the family whose tree is shown in figure 7 was uniformly dominant in the 3 generations on which data were available. Similarly, in the family reported on by Pearson [11] inheritance was dominant in 4 generations. Hansen and von Ubisch [14] maintained that within the same family the type of hereditary transmission is uniform. Grothaus pointed out that the abortive forms of dystrophy often are dominant, and in the family reported on by Manson [15] progression was slow. In the 14 patients reported on here, the onset of the disease was relatively late in life (ages from 28 to 43 years), and the

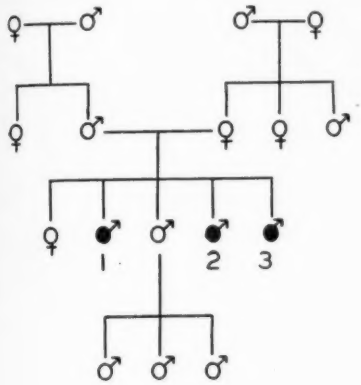

Figure 8

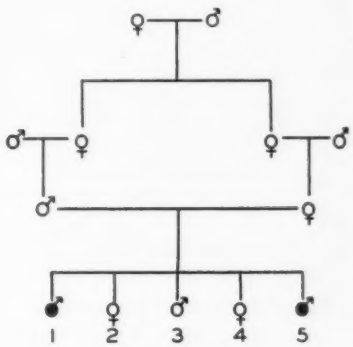

Figure 9

Fig. 8.—In patient *1*, aged 22 years, the condition began at the age of 13 years; he is bedridden. Patient *2*, aged 18 years, walks with difficulty; weakness was first noted at the age of 7 years. In patient *3* the condition started at the age of 14 years; the patient died at 28 years of age, of pneumonia, after being bedridden for four years. The normal male sibling is 30 years old and has 3 sons, the oldest of whom is 5 years of age.

Fig. 9.—The parents are first cousins. There is no known case of muscular dystrophy in the family except those of children *1* and *5*. Patient *1*, aged 21 years, is able to walk only with assistance; symptoms were first noted at the age of 5 years. Patient *5*, aged 17 years, had onset of disability at the age of 5 years; his condition is far advanced. Siblings *2*, *3* and *4* are normal.

symptoms progressed slowly. In a few instances the disease appeared to be abortive. In any event, it is obvious that muscular dystrophy when inheritance is dominant will not be transmitted and therefore will disappear from a family

13. Leiter, A.: Die Andrenalinbehandlung bei progressiver Muskeldystrophie, Monatschr. f. Psychiat. u. Neurol. **81**:289, 1932.

14. Hansen, K., and von Ubisch, G.: Der Erbgang der Dystrophia musculorum progressiva, Deutsche Ztschr. f. Nervenh. **105**:276, 1928.

15. Manson, J. S.: Hereditary Myopathy—A Family Showing Dominant Transmission, Brit. M. J. **2**:1256, 1935.

unless the disability appears relatively late in life or progresses sufficiently slowly to permit some of the patients to marry and have offspring. These considerations probably explain the comparative infrequency of this type of transmission.

The data given in the table show that the type of hereditary transmission of muscular dystrophy could be established for only 40 of the 125 patients in this series. Possible explanations for occurrence of muscular dystrophy in the remaining 85 patients are as follows: (1) The cases were sporadic; (2) the disease was inherited by either a recessive or a dominant factor but was of abortive form in the parents or other members of the family and was unrecognized; (3) heredity was by a simple sex-linked recessive factor, but the fortuitous escape of other members of the family in recent generations prevents determination of the mechanism of inheritance; (4) inheritance was by multiple recessive factors. From the data available on these patients one can only postulate regarding these possibilities. The question whether or not any or all of the cases were of sporadic occurrence can be answered only after all other possibilities have been excluded.

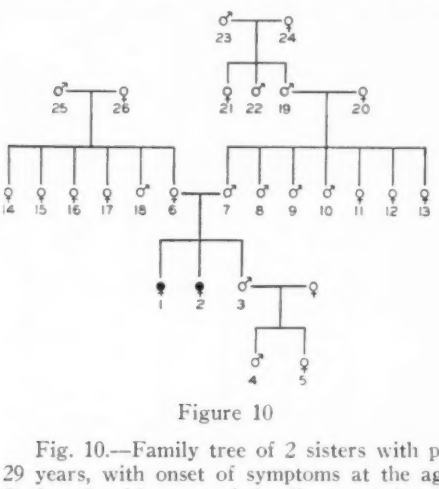

Figure 10

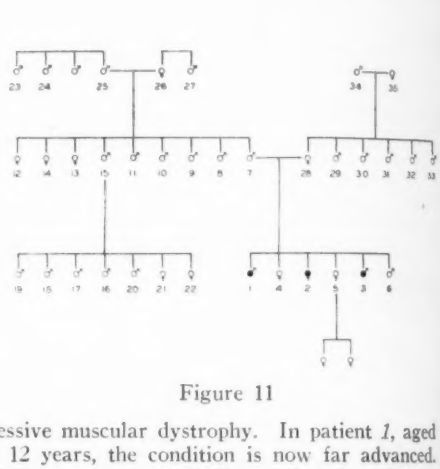

Figure 11

Fig. 10.—Family tree of 2 sisters with progressive muscular dystrophy. In patient *1*, aged 29 years, with onset of symptoms at the age of 12 years, the condition is now far advanced. Patient *2*, with onset of the disease at the age of 11 years, was totally incapacitated at the age of 27 years and died at the age of 33 years. Sibling *3*, a normal male, is 35 years old and has 2 children—*4*, aged 4 months, and *5*, aged 2 years. The mother of the patients (*6*) died at the age of 34 years, with edema. The father (*7*) and his siblings, *8* to *13* inclusive, are living and well at ages ranging from 55 to 68 years; each, except *7*, has several children and grandchildren, who are free from muscular disease. Subject *14* died at the age of 25 years, of heart disease. Subjects *15* to *22* have died, but were free from muscular disease; all had children, all of whom were normal. Subjects *23* to *26* inclusive died at ages ranging from 75 to 99 years and were without muscular disease. The paternal grandfather (*19*) went south with the Union Army, married and settled in Maryland. Since then there have been frequent family reunions. Inquiries among collaterals of the family tree revealed no cases of muscular dystrophy other than those of patients *1* and *2*.

Fig. 11.—In patient *1* the disability started at the age of 8 years and was moderately advanced at the age of 13 years. Patient *2* was always weak; the disease was moderately advanced at the age of 15 years. In patient *3* weakness was first noted at the age of 14 years, and he died when 18 years old. Siblings *4*, *5* and *6*, aged 18, 26 and 22 years respectively, are normal. The father (*7*) is 54 years old. His siblings *8* to *13*, aged 47 to 65 years, have a total of 35 children, all of whom are normal. Subject *15* is his twin brother. The paternal grandfather (*25*) died at the age of 82 years; he was very strong and was said to have been able to carry a load of 400 pounds (181.4 Kg.) on his shoulders when he was 62 years old. The paternal grandmother (*26*) died at the age of 62 years. Subjects *29* to *33*, the mother's siblings, had a total of 15 children, all of whom were normal. The maternal grandfather (*34*) died at the age of 82 years, and the maternal grandmother (*35*), at the age of 80 years.

Weitz[16] expressed the belief that the disposition to the disease arises through mutation in both males and females. This disposition is believed further to be transmitted to half of the descendants and develops into the disease syndrome in the males, and only infrequently in the females. Weitz offered no explanation for the difference in incidence in the two sexes. Diehl, Hansen and von Ubisch[17] rejected the postulation that muscular dystrophy arises by mutation. On the basis of the investigations of Morgan on mutations in Drosophila, these authors expressed the belief that mutations in human beings occur far too infrequently to account for the incidence of muscular dystrophy. Kostakow and Bodarwé[18] referred the occurrence of muscular dystrophy to mutation of heredity factors derived from previous generations. The further inheritance was considered to be by dominant or recessive genes.

Dawidenkow and Kryschowa[19] stated the opinion that muscular dystrophy is transmitted by a dominant factor. They examined the mothers of some patients and found minor structural changes which they concluded to be manifestations of dystrophy. These changes included kyphosis, large calves, flat feet, abdominal hernia, cyanosis of the hands and absence of the achilles reflex. It was postulated that the mothers of patients transmit the disease by a "retarded" dominant factor to 37 per cent of their offspring. While no effort was made in our studies to examine every living forebear of the patients, many were examined and were found to have structural changes of no greater frequency or severity than most persons in whose families dystrophy had never occurred. In our opinion, the validity of one's considering the minor changes described by Dawidenkow and Kryschowa as manifestations of dystrophy is open to serious question. While the postulation of these authors might be an adequate explanation for the occurrence of some "isolated" cases of muscular dystrophy, our observations suggest that most cases cannot be explained on this basis.

The third possibility, that of inheritance by a simple, sex-linked recessive factor, appears to be a mechanism more likely to operate in at least a proportion of the cases. Most of the studies on the heredity of this disease have dealt with material on relatively few generations. In most families, information regarding disease in more than a few generations is either lacking or of dubious value. Therefore, cases of muscular dystrophy can appear to be "isolated" or "sporadic" if other male members of the family in the present and recent generations have fortuitously received the healthy sex chromosome. More complete data might show that males in earlier generations had been affected and thus indicate the sex-linked character of the inheritance. A schematic presentation of this formulation is given in figure 12. It will be noted that 50 per cent of sons of heterozygous mothers could be expected to be affected by the disease, whereas all the sons of a homozygous mother would have the disease. Instances in which the mother could be considered as homozygous were not met with in this series. While the presence of the disease in all sons was seen in certain families, for example, those shown in figures 1 and 2, the mother to be homozygous must be the issue of a male affected with the disease and a female who has transmitted to her daughter a sex chromosome con-

16. Weitz, W.: Der Erbgang der Dystrophia musculorum progressiva, Deutsche Ztschr. f. Nervenh. **102**:209, 1928.

17. Diehl, F.; Hansen, K., and von Ubisch, G.: Der Erbgang der Dystrophia musculorum progressiva, Deutsche Ztschr. f. Nervenh. **99**:54, 1927.

18. Kostakow, S., and Bodarwé, K.: Gibt es einem einkeitlichen Erbgang bei der progressiven Muskeldystrophie? Deutsches Arch. f. klin. Med. **181**:611, 1938.

19. Dawidenkow, S., and Kryschowa, N.: Untersuchungen angeblich gesunder Verwandter von Muskeldystrophikern, Ztschr. f. d. ges. Neurol. u. Psychiat. **125**:31, 1930.

taining the gene for muscular dystrophy. None of the maternal grandfathers of our patients with a recessive type of inheritance had muscular dystrophy. The formulation that in some "isolated" cases of dystrophy the disease is inherited by a simple sex-linked recessive factor could account for the greater incidence of the disease in males.

The fourth possible explanation for the occurrence of "isolated" cases has already been considered by other workers. In fact, Dittrich [20] questioned whether progressive muscular dystrophy can ever be the result of a simple hereditary factor. He stated the belief that the assumption of multiple factors makes comprehensible the various types of the disease. Diehl, Hansen and von Ubisch [17] postulated that

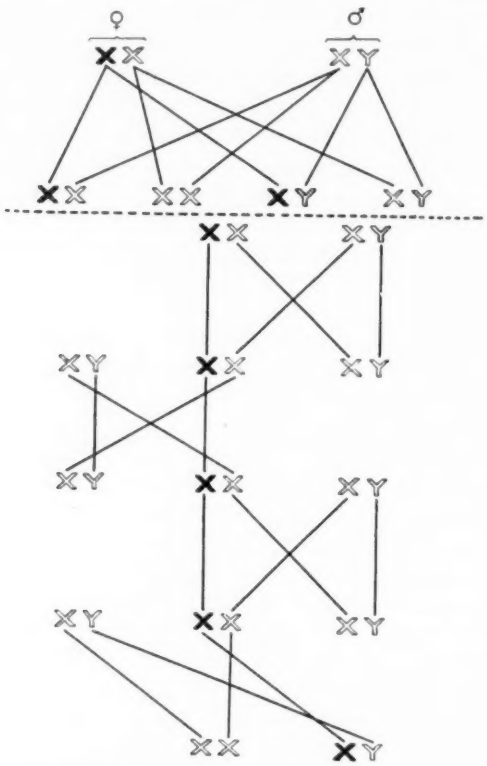

Fig. 12.—Schemas showing simple sex-linked recessive inheritance (based on Morgan [Morgan, T. H.: The Physical Basis of Heredity, Philadelphia, J. B. Lippincott Co., 1919]). The sex chromosome containing the factor for progressive muscular dystrophy is designed as a solid *X*. The normal sex chromosome is shown as *X* in outline. The schema above the dotted line shows transmission of the chromosome containing the disease factor to both males and females in the next generation. The schema below the line shows how male descendants can fortuitously escape the disease for several generations. Since heterozygous females possessing only an affected chromosome will not manifest the disease, the transmission of the chromosome with the factor for dystrophy to a male in the last generation will give rise to so-called isolated, or sporadic, cases of muscular dystrophy.

muscular dystrophy is dependent on two factors, which the authors designated as C and D. Normal persons were considered to have one of the factors (C or D) or neither. Persons with the disease were thought to have both C and D. The

20. Dittrich, R.: Zur Vererbung der progressiven Muskeldystrophie, Verhandl. d. deutsch. orthop. Gesellsch. (1931), 1932, Kong. 26, p. 69.

authors compared their scheme of heredity with that used for the inheritance of blood groups. They concluded that the scheme explains the occurrence of the disease in children of normal parents and the instances in which the transmission of the condition skips one or more generations. However, the scheme does not explain the difference in the number of persons of the two sexes who have muscular dystrophy. The authors expressed the belief that while the influence of sex might theoretically play a role, inheritance could be explained without consideration of sexual influences. Frequent mutations find no place in their scheme. Minkowski and Sidler [21] reported an interesting family tree in which there were 8 males and 5 females who had muscular dystrophy. The family consisted of two branches, the forebears of which had lived in an isolated valley in Switzerland for many generations. There had been numerous intermarriages, and all parents of the patients were blood relatives. The appearance of muscular dystrophy in the families was abrupt, after a long period of intermarriage. Since the disease had been absent in all the forebears, Minkowski and Sidler concluded that its inheritance was of recessive nature. Moreover, the fact that the disease arose only among children of union of the two branches of the family suggested that heredity was by double recessive factors rather than by a single factor.

Multiple hereditary factors have often been described in breeding experiments on animals.[22] Of special interest are the observations of Wood [23] on the inheritance of horns in sheep. Both sexes of the Suffolk sheep are hornless, whereas both sexes of the Dorset sheep are horned, although the horns of the ram are larger. Horned Dorset sheep crossed with hornless Suffolk sheep gave horned sons and hornless daughters. When these offspring were inbred, there were 3 horned males to 1 hornless male and 3 hornless females to 1 horned female. The results can be explained by the assumption that in the male one gene suffices to produce horns, whereas in the female two genes for horns are necessary to produce horns. Therefore in this instance the hereditary factor is sex-limited rather than sex-linked. Among mutants of Drosophila melanogaster several cases of sex-limited characters are found, the effect of a gene on one sex being greater than that on the other.[22] The assumption of a similar mechanism in some cases of progressive muscular dystrophy would go far in explaining the high ratio of males to females (3:1) with this disease. Moreover, the formulation that fewer recessive hereditary factors are required for the development of muscular dystrophy in males than in females suggests the importance of the "sex hormones" on the incidence of this disease.

Macklin [24] expressed the opinion that the variation in modes of inheritance observed in different families could be explained on the assumption that similar clinical entities may be due to diverse pathologic conditions. Application of her formulation to progressive muscular dystrophy implies that among a group of patients with this disease the muscular symptoms are due to one type of process in some persons and to other types in others. In the absence of adequate data on the etiologic factors in muscular dystrophy, this question cannot be answered at present. It is known that certain diseases, such as exophthalmic goiter, can sometimes produce muscular disability that closely resembles muscular dystrophy.

21. Minkowski, M., and Sidler, A.: Zur Kenntnis der Dystrophia musculorum progressiva und ihren Vererbung, Schweiz. med. Wchnschr. **9**:1005, 1928.

22. Morgan, T. H.; Sturtevant, A. H.; Muller, H. J., and Bridges, C. B.: The Mechanism of Mendelian Heredity, New York, Henry Holt & Co., 1923.

23. Wood, T. B.: Inheritance of Horns and Face Color in Sheep, J. Agric. Sc. **3**:145, 1909.

24. Macklin, M. T.: The Role of Heredity in Disease, Medicine **14**:1, 1935.

Askanazy [25] demonstrated considerable muscular involvement associated with exophthalmic goiter, but there could have been little difficulty encountered in making the diagnosis of thyroid disease in the cases reported by him. On the other hand, the 2 patients of Shorr, Richardson and Wolff [26] had muscular disability practically indistinguishable from that seen with progressive muscular dystrophy, and only with the aid of adequate laboratory investigations and a study of the effects of iodine could the diagnosis of exophthalmic goiter be established. Thyroidectomy in both cases induced almost complete restoration of muscular function. Studies of thyroid function were made in practically every case reported in the present series.

Consanguinity of Parents.—In only 1 family (fig. 9) were the parents of the same family stock. In this instance, the mother and father of the 2 patients were first cousins. Blood relationship of parents was stated by Minkowski and Sidler [21] and by Mason and Meloy [27] to be of importance in the families reported on by them.

Relationship of Age of Patient When Symptoms Began and Clinical Course.—An attempt was made to determine the speed of progression of muscular disability and to relate this to the age of the patient when symptoms first were noted.

The amount of muscular disability was estimated by the following criteria:

Observed Limitation in Muscular Function	Estimated Muscular Disability, Per Cent
Slight weakness in arms or legs	10
Waddling gait	15
Arms cannot be raised above shoulder; support needed in arising from floor; patient ascends stairs moving one foot at a time	25
Arms cannot be raised above midthoracic line; patient "climbs up" on thighs in getting up from prone position; ascends stairs holding on to railing	40
Arms cannot be raised above level of waist; patient arises from floor only with great difficulty; stair climbing almost impossible; moderate scoliosis or lordosis	50
Patient unable to get up from sitting position; unable to climb stairs; unable to get up from floor	70
Patient unable to walk; unable to lift arms above level of waist	80
Patient unable to walk, turn over in bed or feed himself; advanced scoliosis or lordosis	90

It is recognized that these values probably do not represent the actual quantitative reduction in total muscular function of the patients. However, it is felt that they do represent the relative impairment of muscular function in the patients in this series and serve a useful purpose for comparison of the different subjects.

When the total muscular disability expressed as the percentage of reduction in muscular function was divided by the number of years during which symptoms had been present, a value representing the average yearly decrease in muscular function was obtained. In figure 13 the average yearly decrease in muscular function in 92 patients is shown in relation to the ages at which muscular symptoms began.

25. Askanazy, M.: Pathologisch-anatomische Beiträge zur Kenntnis des Morbus Basedowii insbesondere über die dabei auftretende Muskelerkrankung, Deutsches Arch. f. klin. Med. **61**: 118, 1898.

26. Shorr, E.; Richardson, H. B., and Wolff, H. G.: Unpublished observations; patients presented before the Section of Medicine, New York Academy of Medicine, Dec. 17, 1940.

27. Mason, W. S., and Meloy, R. C.: Progressive Muscular Atrophy: Five Cases in One Family, J. Oklahoma M. A. **23**:265, 1930.

The data show that when the disease began in the first decade of life the clinical course was rapid; in most instances the average yearly loss in muscular function was 13 per cent. When the onset of symptoms appeared during the second decade, the progress of the disease was slower, the yearly loss in function averaging about 7 per cent, and when the onset was in the third decade the average progression in disability was only about 3 per cent per year. There were significant differences among the patients in most of the age groups: for example, in a patient in whom the symptoms began at the age of 7 years, the yearly increase in disability was only 5 per cent, whereas in another patient it was 18 per cent. The average value for the 10 patients in this age group was about 12 per cent. Therefore, while the data in this series can be used in a general way in the prognosis for a patient with muscular dystrophy, the prediction applies only to the average for the patients in the same group. These observations confirm the opinion stated by Gowers,[1] Voshell [10]

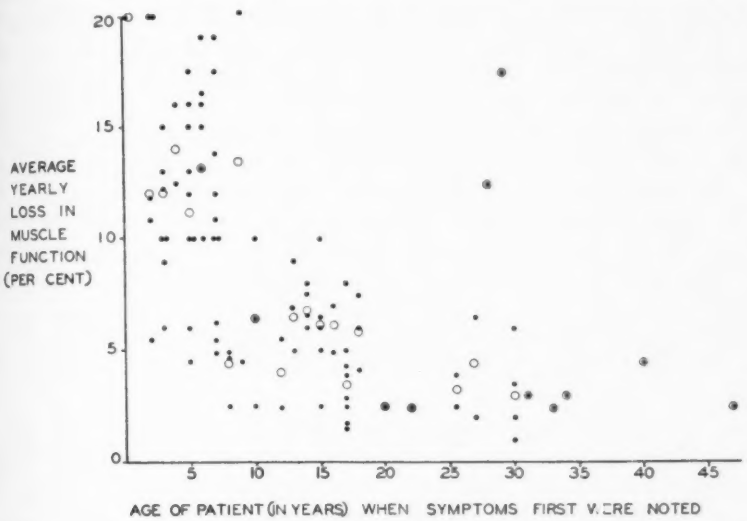

Fig. 13.—Relationship between progression of disability and age of patient when muscular symptoms first were noted, in 95 cases. The dots represent data on individual patients; the open circles, average values for the different age groups.

and Hurwitz [3] that the earlier in life symptoms of muscular dystrophy develop the more rapid the progression of disability is likely to be.

It can also be stated that, in general, the age of onset of the disease was approximately the same in all patients in any one family, although this age of onset showed considerable variations among the different families. Moreover, the rapidity with which the muscular symptoms progressed was roughly similar in patients in the same family. Macklin [28] stated her belief that these phenomena apply to most hereditary diseases.

SUMMARY

The heredity of progressive muscular dystrophy was studied in 75 families, in which a total of 125 members were affected with the disease. On 85 of these

28. Macklin, M. T.: The Relation of the Mode of Inheritance to the Severity of an Inherited Disease, Human Biol. **4**:69, 1932.

patients clinical and chemical studies were made, in most instances at frequent intervals over periods of several years. The observations were as follows:

1. Fifty-four per cent of the 125 patients gave a history of at least 1 other member of the family affected with the disease; of the 85 patients who were examined, 25 per cent gave a positive familial history of the disease.

2. More males had progressive muscular dystrophy than did females. The ratio of males to females was 3 : 1.

3. Twenty-six males inherited the disease by a simple sex-linked recessive factor; e. g., the muscular dystrophy appeared in the males but was transmitted by apparently healthy females.

4. In 7 males and 7 females transmission of the disease was by a dominant hereditary factor.

5. The exact mechanism of heredity in 61 males and 24 females was not determined, but was of a recessive type. The ratio of males to females in this group was 2.5 : 1. It is postulated that in this group inheritance in many instances was by a simple sex-linked recessive factor. The sex chromosome carrying the dystrophy factor probably was transmitted by the females of the family for a number of generations without transmission to a male other than the patient and his siblings. The fortuitous absence of the disease in the male members of previous generations on which information is available would mask this type of hereditary transmission. However, it is unlikely that this mechanism accounts entirely for the frequency of the disease among males. Another possible type of hereditary transmission is one of multiple recessive factors in which the number of factors necessary to induce the condition is fewer for males than for females. A similar influence of sex on the number of hereditary factors required for certain characteristics has been demonstrated in many species of animals. The influence of sex on the incidence of progressive muscular dystrophy might be of importance in the concept of the mechanism and cause of the condition.

6. There was a definite relation between the age of the patient when the symptoms first were noticed and the clinical course of the disease. In patients in whom the disease appeared early in life disability developed much faster than it did in patients in whom the first symptoms appeared at a later age.

7. In the present series, the patients whose inheritance of the disease was by a dominant hereditary factor manifested their first symptoms relatively late in life. In these patients the progress of the disease was slow, and investigations showed that the disease remained localized to certain muscle groups for long periods.

8. In contrast, when progressive muscular dystrophy developed early in life the process usually became extensive in distribution and involved most of the muscles early in the course of the disease.

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STUDIES IN DISEASES OF MUSCLE

XIII. PROGRESSIVE MUSCULAR DYSTROPHY OF ATROPHIC DISTAL TYPE; REPORT ON A FAMILY; REPORT OF AUTOPSY

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In the preceding report in this series [1] reference was made to a family in which 12 members had progressive muscular dystrophy with inheritance by a single dominant hereditary factor. The data on heredity were illustrated in figure 7 of that report.

The symptoms, clinical observations and changes in creatine metabolism, as well as the inheritance of the disease in members of this family, were so unusual for progressive muscular dystrophy that a presentation of case histories appears desirable. In many respects the clinical picture resembled that of Charcot-Marie peroneal muscular atrophy, in which transmission of the disease usually is by a dominant hereditary factor.[2] Since this family contained 12 of the 14 patients in the entire series in whom inheritance was by a dominant factor, it seemed of importance to the general problem of muscular disease, especially the heredity of progressive muscular dystrophy, to determine whether these patients had muscular dystrophy or whether the muscular disease was peroneal muscular atrophy. Most of the patients were followed for a period of seven years. During this entire time, it was impossible to be certain of the diagnosis until a complete necropsy was made in 1 case.

Six cases, with the observation at autopsy in 1 of them, are reported. The numbers assigned to the cases are those used in the family tree in the previous report.[1]

REPORT OF CASES

CASE 3.—*History.*—The patient was not examined by us. She was hospitalized at the Montefiore Hospital, New York, from July 10 to Nov. 10, 1923. The director of the hospital supplied the following information: A housewife aged 38 was admitted on July 10, 1923, complaining of weakness of the lower extremities and difficulty in walking. Her illness began ten years before her admission, when she first noted pain and a feeling of tiredness in both thighs and legs. Her legs gradually became weaker, and she tired excessively on walking. Later she noted difficulty in raising the legs and had to "pick them up with her hands and place them on a chair" when attempting to put on her stockings or shoes. She soon noted difficulty in arising from the floor when she was scrubbing unless she assisted herself by firmly grasping surrounding objects. Her walking became progressively more difficult and unsteady up to the time of admission.

The past history was noncontributory.

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From the Departments of Medicine and Psychiatry, Cornell University Medical College; the Russell Sage Institute of Pathology, and the New York Hospital.

1. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: XII. Heredity of Progressive Muscular Dystrophy; Relationship Between Age at Onset of Symptoms and Clinical Course, Arch. Neurol. & Psychiat., this issue, p. 641.

2. Small, S. M., and Milhorat, A. T.: Studies in Diseases of Muscle: VI. Progressive Peroneal Muscular Atrophy; Report on a Family, with Study of Heredity and Metabolism of Creatine and Creatinine, Arch. Neurol. & Psychiat. **40**:911 (Nov.) 1938.

Examination.—The patient was a middle aged woman, who appeared fairly well nourished. She walked with a waddling gait, with abdomen thrown forward and compensatory lordosis. In rising from a recumbent position she supported herself by placing her hands on her knees. The left pupil was slightly larger than the right, but both reacted to light and in attempts at her near vision. Motor power in the upper extremities appeared to be normal. The tendon reflexes in the upper extremities were hyperactive and equal on the two sides. There were no pathologic reflexes. The biceps and deltoid muscles appeared to be slightly underdeveloped. As compared with the thighs both legs appeared smaller than normal, and the wasting was more pronounced in the muscles below the knees. The left calf measured 11¾ inches (29.9 cm.) in circumference and the right calf 11½ inches (29.2 cm.). There was atrophy of the muscles of the thighs. The circumference of the right thigh was 14½ inches (36.8 cm.) and that of the left 15 inches (38.1 cm.). Weakness was moderate in the hamstring group of muscles on the left side and slight on the right. Foot drop, with inversion of the left foot, was present bilaterally. The patient could move the toes. The only reflex obtained in the lower extremities was the patellar, which was sluggish bilaterally, but a little more active on the left side. The abdominal reflexes were present. No fibrillations were observed. There were no sensory defects. The Wassermann reaction of the blood was negative. Roentgenograms of the spine and skull showed nothing abnormal.

The diagnosis was progressive muscular dystrophy (atrophic type).

Subsequent Course.—The muscular disability progressed steadily, and the patient died in 1934, at the age of 49 years.

CASE 5.—*History.*—A widow aged 67 had extensive muscular wasting of many years' duration. She stated that at about the age of 43 she first noted weakness of the feet. The symptom was insidious in onset and was slowly progressive. A few years later the muscles of the hands and calves were affected. The process in the upper extremities gradually extended to the muscles about the shoulders. There was no pain or paresthesia. She was seen on Feb. 19, 1934, when the results of examination were about the same as those obtained on Jan. 22, 1941, to be described, except that muscular wasting was not as advanced and she was able to walk with assistance. In 1936 the patient tripped and fell, sustaining a fracture of the lower end of the femur. This necessitated a prolonged period of rest in bed, and thereafter she was unable to walk again.

Examination (Jan. 22, 1941).—The patient sat comfortably in bed but was unable to raise the arms more than a few inches from the side of the body. The pupils were equal and regular and reacted normally to light, but there was little reaction in attempts at near vision. The movements of the eyeballs were limited in attempts at convergence; otherwise, the extraocular movements were normal. Examination of the fundi showed the disks to be normal, but there was considerable sclerosis of the retinal arteries. There was no weakness of the face. The tongue showed no wasting or fibrillations. Gross power of all the muscles of the upper extremities was greatly reduced. The patient was able to exert little resistance to passive flexion or extension of the upper extremities. She could lift the arms only a few inches from the side of the body. Muscular wasting was moderate in the upper portions of the arms, more definite in the forearms and fairly advanced in the hands. There was atrophy of the thenar and hypothenar eminences and of the intrinsic muscles of the hands. The grip was weak, and approximation of the thumb and index finger was feeble. The hand presented a moderately advanced main en griffe appearance. The finger nails had numerous ridges extending the length of the surfaces. The patient stated that this condition had been present for about five years. There was slight wasting of the muscles about the shoulders, but no definite flaring of the scapulas could be seen. The lower extremities were very weak, and the patient was practically unable to make any movements with them. There was a definite bilateral foot drop, and the feet could not be brought from this position even when considerable force was applied by the examiner. The patient was unable to move the toes. The feet were flat and wasted. There was considerable weakness of the thighs, and the lower extremities could be flexed or extended at the hip without much difficulty by the examiner even when the patient exerted all possible power. The muscles of the peroneal and tibial groups appeared to be of normal size. They had a rather hard feel, with a doughy character. The skin over the hands and feet was smooth and shiny. The tendon reflexes in the upper extremities were active; in fact, they suggested some hyperactivity, but there was no finger stretch reflex. The patellar and achilles reflexes were absent. The plantar response was flexor in type. There was moderate diminution in vibration sense over the toes of both feet. Sensibility for pain, light touch and position was normal. There were no fibrillations.

The patient experienced considerable dyspnea and weakness when she attempted to sit up with her feet hanging over the side of the bed. After the feet had hung for an hour or so, definite edema of the ankles developed. The heart was enlarged; the rate was rapid, and there were numerous premature contractions. The picture was one of arteriosclerotic heart disease.

Formulation.—Examination at this time showed essentially the same condition as that noted seven years previously. There had been little progression in the muscular disability except that occurring subsequent to the fracture of the leg and the prolonged rest in bed necessitated by treatment of the fracture. The foot drop and the contractures of the feet probably were due to prolonged inactivity and the weight of the bedclothes on the feet.

Subsequent Course.—During the last week of November 1941 pain developed in the abdomen. This pain came on acutely, was rather severe and persisted for a few days. The patient then continued in about the same condition as prior to this episode. About December 13 she had

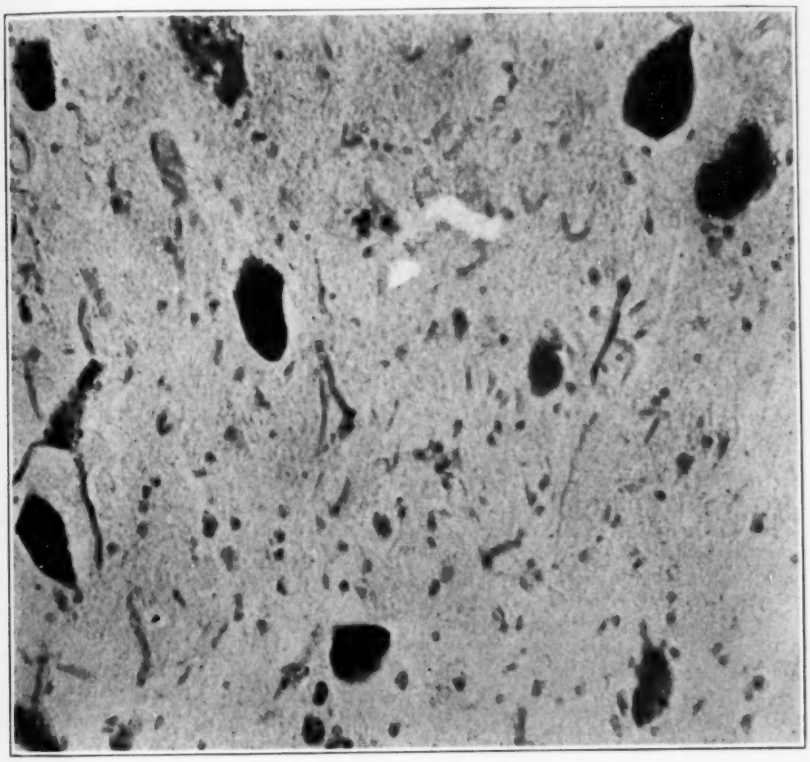

Fig. 1 (case 5).—Motor ganglion cells of the anterior horn, midcervical level (description in text).

a recurrence of abdominal pain, which came on acutely, was very severe and persisted. The patient gradually became comatose and died on Dec. 20, 1941.

Autopsy, by Dr. L. D. Stevenson and Dr. D. P. McEndy, of the department of pathology, was performed twelve hours after death.

Gross Examination.—Inspection: The body was that of a white woman, which measured 152 cm. in total length and weighed 48 Kg. It was poorly developed but moderately well nourished. There was only a slight amount of rigor mortis of the upper extremities; none was observed in the lower extremities or the neck. There was considerable loss of subcutaneous fat, particularly in the upper extremities. The muscle tissue about the shoulder girdle and the upper and lower portions of the arms was slight in amount, soft and flabby. The supraspinatus and infraspinatus muscles were almost completely absent. The spines of the scapulas were conspicuous throughout their entire length, and the bodies of the scapulas could easily be palpated. The muscles of the flexor surfaces of the forearms were considerably

decreased in size. The fingers and hands were held in a semiextended position. No rigor mortis was observed in the fingers, but they tended to assume a perfectly straight plane. The general outlines of the lower extremities and of the pelvis were within normal limits. No such atrophic picture as was seen in the upper extremities was present here. There was moderate edema of the legs, ankles and feet. The feet were plantar flexed and everted outward. The skin over the anterior surface of the legs was thin and shiny, and there was a mottled pink discoloration of the skin in these regions and over the anterior surfaces of the thighs. The thigh muscles were soft and flabby, but not to an extent comparable to that observed in the upper extremities.

Muscles: The muscles of the body that were examined were smaller than normal and paler than is usually seen. This was noted particularly in the rectus abdominis muscles and in the muscles of the neck and shoulders. Those of the upper portions of the arms were observed to be in a similar condition, but less pale.

Brain and Spinal Cord: The skull was thick, and irregularly so. Neither the pachymeninges nor the leptomeninges showed change. The venous sinuses were patent. The cranial nerves and the pituitary were not remarkable. Nothing unusual was noted in examination of the accessory nasal sinuses or of the middle and internal ears.

The vessels of the circle of Willis were moderately sclerotic. There were two small whitish nodules on the under surface of the dura of the upper parietal region on the left side. One measured approximately 1 cm. and the other approximately 0.5 cm. in diameter. Both were rather flat. There was fairly extreme cortical atrophy of both hemispheres, particularly in the frontal and parietal regions and to a lesser extent in the temporal region. No evidence of internal hydrocephalus was noted. There was no softening or hemorrhage into the brain substance. No lesion was visible in the basal ganglia or in the internal capsule.

An area of flattening, possibly an artefact (?), was present in the upper thoracic region of the spinal cord, just below the cervical region. There was considerable congestion of the capillaries of the gray matter of the thoracic and lumbar regions of the cord.

Microscopic Examination.—Muscle: A section taken through the rectus abdominis muscle showed this tissue to be almost completely replaced by fat. The few strands of muscle that remained stained very lightly, but their cross striations persisted. Between the muscle fibers in some places were collections of cells with dark, round and spindle-shaped nuclei.

Only small collections of fat were seen in a section taken from the biceps muscle, but the muscle fibers took a very pale stain. The cross striation remained. A similar, but less extreme, picture was seen in a section through the psoas muscle. Here the fibers were scanty, and considerable fat was seen between them in some places.

Brain and Spinal Cord: A section of the precentral gyrus stained by the Nissl method showed that the Betz cells were well preserved and the other cortical layers normal in appearance, although there was slight dropping out of cells. A section of the spinal cord in the midcervical region showed no loss of myelin. The anterior horn cells were normal in number, but they gave evidence of atrophy, with tortuous processes and deeply staining cytoplasm (fig. 1). In a similar section through the upper thoracic region the nerve cells of the anterior horns presented the same appearance. In the upper lumbar region pyknosis of the anterior horn cells and other atrophic changes were apparent. In the sacral region the condition of the anterior horn cells was similar. It is likely that these changes in the anterior horn cells throughout the spinal cord were the result, rather than the cause, of muscular disease. A section of the right femoral nerve stained for fat showed no degenerative change.

Additional Autopsy Observations: There were multiple healed infarcts of the spleen and kidneys; embolism of the abdominal aorta and iliac, superior mesenteric and celiac arteries; massive infarction of the terminal portion of the jejunum and of the proximal half of the ileum; serofibrinous peritonitis; bilateral hydrothorax; partial atelectasis of the lower lobes of both lungs; passive congestion of the liver, with fatty degeneration and beginning cirrhosis; advanced arteriosclerosis of the thoracic and abdominal portions of the aorta; moderate arteriosclerosis of the cerebral, coronary, mesenteric, splenic and common iliac arteries; slight fibrosis of the myocardium; fibrous pleural adhesions at the apex of the left lung; calcified nodules in the lower lobe of the left lung and in corresponding peribronchial lymph nodes; small cysts of both kidneys; hemangioma of the spleen, and mucus cysts of the fundus of the uterus.

CASE 8.—*History.*—A housewife aged 38 was first seen in the clinic on Nov. 16, 1934, with the complaint of difficulty in walking, of one year's duration. The patient stated that up to the age of 28 years she had no difficulty whatever in walking, but thereafter there was a gradually increasing sense of heaviness in the feet. This symptom was mild until about one year prior to her admission to the outpatient department, when it increased definitely. She found it necesesary to be careful while walking, since she showed an increasing tendency to trip.

Examination and Clinical Course.—Examination showed the gait to be somewhat steppage in type, but there was no lordosis or other abnormality. Examination of motility showed no

abnormality except in the muscles below the knees. The calves were somewhat large and of wooden consistency. The feet were held moderately overextended. Extension of the feet appeared to be only slightly impaired, whereas flexion of the feet was weak. The tendon reflexes were active and equal on the two sides except for the ankle jerks, which were definitely reduced. Sensory function was normal. The patient weighed 69 Kg.

In July 1935 the patient visited another hospital, where a lumbar puncture was performed. After this procedure headache developed, and it was necessary for her to remain in bed about four weeks. During her prolonged period of inactivity the weakness of the feet progressed rather rapidly, and for the next three months she complained of pain in both feet whenever she walked. With the help of physical therapy the condition gradually improved and by the end of another month was about the same as before the lumbar puncture.

Subsequent Course.—During the next six years the condition of the patient was slowly progressive.

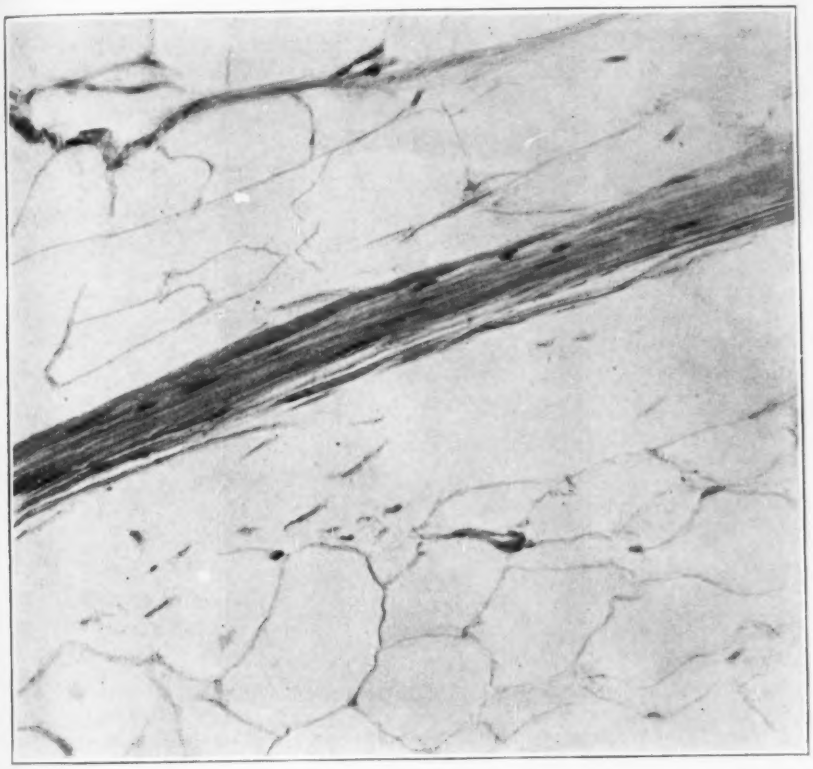

Fig. 2 (case 10).—Muscle removed post mortem from thigh (description in text).

CASE 10.—*History.*—A man aged 38 was first observed at the New York Hospital on Dec. 9, 1933. In 1926, at the age of 30, he began to have difficulty in raising his thighs. This gradually became worse, and in 1929 he had difficulty in extending his feet. In 1932 he was seen in another hospital, where a diagnosis of progressive muscular dystrophy was made.

Examination.—There was weakness of the iliopsoas muscles and of the lower extremities. The peroneal muscles were weak, although the calves were large. The muscles of the left calf were of wooden consistency. There was no definite wasting of the muscles of the upper extremities, but the left biceps muscle was weak and there was slight winging of the scapulas. There was no sensory defect. The patient weighed 79 Kg.

Clinical Course.—The muscular weakness and wasting gradually increased. Twelve years after the onset of the disability the patient had considerable difficulty in getting about. In 1938 he fell and sustained a fracture of the shaft of the femur. The fracture healed in normal manner, but thereafter the patient was unable to walk. In December 1939 pneumonia developed, and he died.

Examination of Muscle.—A piece of muscle removed post mortem from the right thigh by Dr. Ben Klotz was sent to us for examination. The report of the microscopic examination by Dr. N. C. Foot, of the department of surgical pathology, follows:

"Microscopic examination of the muscle tissue revealed the most profound changes yet seen in this laboratory. The main bulk of the tissue was rather normal-appearing fat, and one would not have suspected that muscle had been present until several strands of fibrous tissue containing much degenerated, but quite definite, striated muscle were encountered. In some portions these remains of striated muscle took a greenish color rather than the hematoxylin stain, indicating a changed reaction. These strands were short and faded into the fibrous tissue (fig. 2). Apparently, the sarcolemma cells remained somewhat longer than the other constituents. At various points there were small collections of lymphocytes, usually strung out in single or double file, paralleling the muscle strands. Dilated vessels were seen here and there.

"The diagnosis was progressive muscle dystrophy, terminal stage."

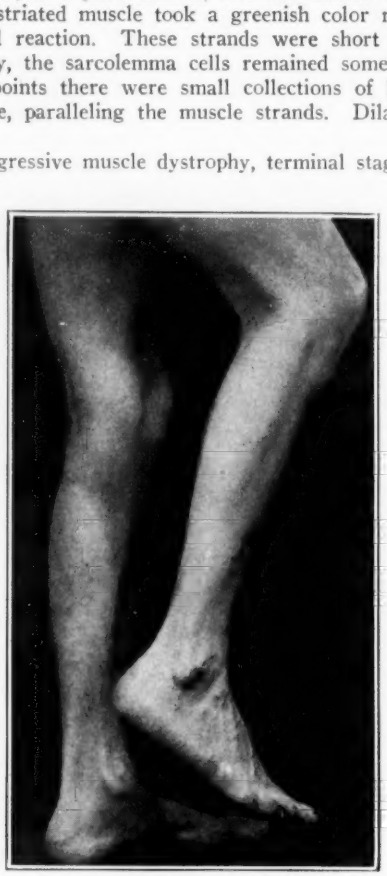

Fig. 3 (case 11).—Wasting of muscles below the knees. These changes were typical of all patients in this family during the moderately early stages of the disease.

CASE 11.—*History.*—A man aged 37, a theatrical agent, complained of difficulty in walking. About four years prior to his admission to the hospital, on Jan. 19, 1939, he noted that his feet made a slapping sound when he walked. This was noticed also by his friends, who frequently called his attention to it. About two years after the onset of this symptom the patient began to stumble over low objects, such as irregularities in the pavement, and on several occasions he fell. For about one and one-half years prior to his admission he noted a gradual increase in weakness of the calves and thighs. He was able to walk for only short distances and had to hold on the railing with his hands while ascending stairs. For one year he had cramplike pains in the left foot, and on occasion this foot felt numb. The patient stated the belief that the muscular weakness had been limited to the legs.

Examination.—The patient lifted his feet high while walking and brought them to the floor with a loud slapping sound. When the lower end of the tibia was grasped and the leg shaken, the foot seemed to be only loosely attached. The feet were kept in an overextended position, and the patient was unable to flex them. There were definite wasting of all muscles below the knee and slight weakness, but no wasting, of the muscles of the thighs (fig. 3).

The tendon reflexes were normal except that the knee and ankle jerks on the left side were slightly diminished. Sensory function was unimpaired.

Subsequent Course.—The patient was seen at frequent intervals during the next two and one-half years. During this period there was only slight increase in disability.

CASE 12.—*History.*—A male clerk aged 30 was first seen in the clinic on Jan. 16, 1939. He stated that for a few months he had noticed slight difficulty in walking, with a tendency to stumble over low objects. The symptoms had been mild, but the patient consulted a physician because his brother had had increasing difficulty in walking and the patient was apprehensive that he might be acquiring the same condition.

Examination.—At the time of the first visit to the clinic examination disclosed no evidence of muscular disease. The patient was seen again in May 1940, with a history that the difficulty in walking had increased slowly but progressively. At that time there was slight atrophy of the muscles of the calves and feet. There was no involvement of the muscles elsewhere. Sensory function was normal.

Subsequent Course.—The patient was seen on numerous occasions, and during the past year muscular disability had progressed slowly. At the time of writing the patient raised his feet rather high while walking and brought them to the floor with a slapping sound. There was definite weakness in flexion of the feet. The muscles of both feet and calves showed moderate wasting, somewhat more definite on the left side.

In August 1942 definite enlargement of the left calf was observed. Apparently, this change had occurred rather suddenly. The appearance and consistency of the calf had many characteristics of pseudohypertrophy, but the slight pitting produced by pressure in the lower portions of the calf suggested that the change in size was due to edema.

CASES 1, 2, 4, 6, 7 and 9.—The patients were not examined by us. Information obtained from other members of the family included the following data:

Patient 1, the earliest male in the family on whom data could be ascertained, had weakness and wasting of the muscles of the legs and feet but was able to walk until the time of his death, at the age of 55 years.

In patient 2 symptoms first were noted in the legs at the age of 26 years. The disability progressed steadily, and the shoulders were affected a few years later. The patient was incapacitated when she was about 35 years old, and she died at the age of 45.

Patient 4 had muscular disability similar to that of patient 3. Onset was at the age of 30 years. At the age of 35 she was incapacitated, and at the age of 45 she died.

Patients 6, 7 and 9 first noted symptoms in the legs and feet at the ages of 38, 28 and 28 years respectively.

METABOLISM OF CREATINE AND CREATININE

The metabolism of creatine and creatinine was studied in 4 of the patients by the methods described previously.[3] In 3 of the patients the output of creatinine was reduced only moderately and in proportion to the reduction in muscular mass; spontaneous creatinuria was minimal, and the creatine tolerance was essentially normal. These results are similar to those observed in patients with wasting limited to relatively few muscle groups, such as muscular wasting subsequent to disease of the nervous system.[4] In the family with progressive peroneal muscular atrophy reported by Small and Milhorat[2] the changes in the metabolism of creatine and creatinine were identical with those in the present 3 patients. However, in 1 patient (case 10), a man weighing 79 Kg., the daily output of creatinine was only 0.858 Gm. and the spontaneous output of creatine was 0.200 Gm. daily. These results are similar to those obtained for patients with widespread muscular involvement.

The essential facts regarding this syndrome can be summarized as follows: The onset occurs relatively late in life, usually about the end of the third decade.

3. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: I. Metabolism of Creatine and Creatinine in Progressive Muscular Dystrophy, Arch. Neurol. & Psychiat. **38:** 992 (Nov.) 1937.

4. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: IV. Metabolism of Creatine and Creatinine in Muscular Wasting Subsequent to Disease of the Nervous System, Arch. Neurol. & Psychiat. **40:**663 (Oct.) 1938.

The muscles earliest and most severely involved are those of the peroneal and tibial groups. Progression of disability usually is slow; occasionally, after a period of a few years the muscles of the shoulder girdle or the hands are involved. Sensory defects and fasciculations are absent. The tendon reflexes are reduced or absent. In 2 instances enlargement of the calves suggested pseudohypertrophy; in another case one calf was increased in volume, as a result of edema.

Microscopic examination of muscles in 2 cases of advanced dystrophy showed almost complete replacement of muscle fiber by fat, with preservation of cross striations in the few remaining muscle fibers. In 1 case studied at autopsy microscopic examination of the spinal cord at different levels showed that the anterior horn cells were normal in number but had undergone atrophic changes, which were interpreted as being the result, rather than the cause, of muscular disease. No microscopic changes in the peripheral nerves were seen.

Cases of muscular dystrophy with involvement primarily of the distal muscles were reported by Gowers, Spiller, Batten, Oransky, Barnes and others. Gowers [5] described a distal form of muscular dystrophy in 2 cases. In his first case, that of a youth aged 18 years, with a negative familial history for the disease, onset of symptoms was at the age of 12. The affected muscles were those of the lower portions of the legs and the hands, forearms and face. The calves were sufficiently large to suggest pseudohypertrophy. In Gowers' second case, that of a woman aged 23, symptoms began at 16. Three sisters were similarly affected, but no other instance in the family could be found. The muscles of the shoulder girdle and the entire upper extremities, including the hands, were wasted. In the lower extremities wasting was limited to the muscles below the knees. Gowers pointed out that in both cases the involvement of the legs was purely distal.

In Spiller's [6] case, that of a man aged 50, symptoms had started thirty-five years previously with pains in the legs and feet. The patient noted no weakness until the age of 35 years, when the legs were observed to be getting thinner and somewhat deformed. Ten years later wasting of the muscles of the forearms and hands was noted. Muscular wasting progressed steadily but remained limited to the portions distal to the knees and elbows. The patient was unable to work after the age of 50 years. Sensory function was normal.

Batten [7] reported cases which he called instances of a distal type of muscular dystrophy. In his first case, that of a youth aged 18, wasting of the muscles of the forearms, legs and thighs was present. In his second report Batten described a family in which muscular atrophy was limited to the portions below the knees. He emphasized the difficulty of distinguishing cases of this type from those of muscular atrophy of the peroneal type.

Oransky [8] described an unusual form of muscular dystrophy in which the muscles of the shoulder girdle and peroneal groups were wasted. In some instances the muscles of the hands and the distal portions of the thighs were affected. Sensory function was normal. The disease began at the age of 18 to 20 years, and the course was slowly progressive. Six males and 4 females in four generations were affected. Heredity was by a dominant factor.

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5. Gowers, W. R.: A Lecture on Myopathy and a Distal Form, Brit. M. J. **2**:89, 1902.

6. Spiller, W. G.: Myopathy of the Distal Type and Its Relation to the Neural Form of Muscular Atrophie (Charcot-Marie-Tooth Type), J. Nerv. & Ment. Dis. **34**:14, 1907.

7. Batten, F. E.: Distal Type of Myopathy, Proc. Roy. Soc. Med. **3**:92, 1909-1910; Distal Type of Myopathy in Several Members of a Family, ibid. **3**:93, 1909-1910.

8. Oransky, W.: Ueber einen hereditären Typus progressiver Muskeldystrophie, Deutsche Ztschr. f. Nervenh. **99**:147, 1927.

Dawidenkow [9] observed a syndrome characterized by muscular atrophy of the Charcot-Marie type in the lower extremities and by wasting of the muscles of the shoulder girdle and the proximal muscles of the upper extremities. Several of the patients had thick fleshy lips similar to the condition seen in muscular dystrophy. In addition to his own cases, he collected several from the literature, including those of Oransky, which he concluded belonged to the same category. In Dawidenkow's cases there was hypesthesia of distal distribution in all four extremities, and heredity was by a dominant factor.

In the family reported by Barnes [10] muscular atrophy was limited to the distal portions of the upper extremities. Moreover, the hypertrophy and pseudohypertrophy that preceded the atrophy make it exceedingly unlikely that the condition was identical with that seen in our patients.

Hoffmann and Clauss [11] reported observations on an interesting family in which 8 members, in three generations, were affected with muscular disability that resembled a combination of dystrophy and progressive spinal muscular atrophy of the Duchenne-Aran type.

Rimbaud and Giraud [12] described the cases of 3 brothers presenting a distal type of muscular dystrophy with onset at about puberty. The early development of contractures sharply distinguishes these cases from ours, in which no contractures occurred, except in case 5, in which the contractures developed as a result of prolonged inactivity. On the other hand, the cases described by Gowers and Oransky in many ways resembled those in the present report.

The observations at autopsy were more typical of those of progressive muscular dystrophy than of Charcot-Marie muscular atrophy, peripheral polyneuritis or progressive spinal muscular atrophy. Whereas the spinal cord is often entirely normal in cases of progressive muscular dystrophy (Middleton,[13] Schultze,[14] Landouzy and Dejerine,[15] Spiller [6] and Friesz [16]), slight or moderate changes, particularly in the ganglion cells of the anterior horns, have been reported by many observers.

Alterations in the ganglion cells of the anterior horns in the nature of degenerative changes or diminution in the number of motor cells were reported by Erb and Schultze,[17] Pekelharing,[18] Gibney,[19] Frohmaier,[20] Lorenz,[21] Foix and Nicolesco,[22]

9. Dawidenkow, S.: Ueber die scapulo-peroneale Amyotrophie. (Die Familie "Z"). Ztschr. f. d. ges. Neurol. u. Psychiat. **122**:628, 1929; Scapuloperoneal Amyotrophy, Arch. Neurol. & Psychiat. **41**:694 (April) 1939.

10. Barnes, S.: A Myopathic Family, with Hypertrophic, Pseudohypertrophic, Atrophic and Terminal (Distal in Upper Extremities) Stages, Brain **55**:1, 1932.

11. Hoffmann, H., and Clauss, O.: Klinischer und erbbiologischer Beitrag zur Lehre von der Muskeldystrophie (Kombination von Erbscher Dystrophie mit spinaler progressiver Muskelatrophie), Ztschr. f. d. ges. Neurol. u. Psychiat. **106**:312, 1926.

12. Rimbaud, L., and Giraud, G.: Myopathie familiale du type péronier ou distal, Rev. neurol. **28**:1004, 1921.

13. Middleton, G. S.: On the Pathology of Pseudo-Hypertrophic Muscular Paralysis, with Remarks on a So-Called Degeneration of the Nervous System, Glasgow M. J. **22**:81, 1884.

14. Schultze, F.: Ueber den mit Hypertrophie verbundenen progressiven Muskelschwund und ähnliche Krankheitsformen, Wiesbaden, J. F. Bergmann, 1886.

15. Landouzy, L., and Dejerine, J.: Nouvelles recherches cliniques et anatomo-pathologiques sur la myopathie atrophique progressive à propos de six observations nouvelles, dont une avec autopsie, Rev. de méd. **6**:977, 1886.

16. Friesz, J.: Beitrag zur anatomischen Kenntnis der Muskeldystrophie, Deutsche Ztschr. f. Nervenh. **112**:318, 1930.

17. Erb, W., and Schultze, F.: Ein Fall von progressiver Muskelatrophie mit Erkrankung der grauen Vordersäulen des Rückenmarks, Arch. f. Psychiat. **9**:369, 1879.

18. Pekelharing, C. A.: Ein Fall von Rückenmarkserkrankung bei Pseudomuskelhypertrophie, Virchows Arch. f. path. Anat. **89**:228, 1882.

(Footnotes continued on next page)

Poinso and Poursines [23] and others. In the case reported by Ballet and Laignel-Lavastine [24] muscular disability had been present about twenty years; at autopsy the motor cells of the anterior horns showed simple atrophy and considerable diminution in number. In the case reported by us the comparatively minor changes in the anterior horn cells can be interpreted as the result of muscular atrophy of long duration; certainly, they appeared insufficient to account for the advanced muscular wasting.

In brief, it can be stated that whereas the nature of the lesion in progressive muscular dystrophy is not known, the condition can be regarded as primarily affecting the muscles. However, in certain cases, especially those in which the muscular wasting has been of long standing, slight or moderate changes in the spinal cord are observed which are interpreted as being the result, rather than the cause, of the muscular atrophy. The alterations in our case, interpreted in the light of this formulation, are considered to be those of progressive dystrophy.

SUMMARY

A family in which progressive muscular dystrophy of atrophic distal type developed in 12 members is reported. The onset of symptoms usually was at about the age of 33 years (from 28 to 43 years). The muscles earliest and most severely affected were those of the legs and feet. Heredity was by a dominant factor. Autopsy observations in 1 case were similar to those often made in cases of progressive muscular dystrophy.

525 East Sixty-Eighth Street.

19. Gibney, V. P.: Is There a Primary Cord Lesion in Pseudohypertrophic Paralysis? J. Nerv. & Ment. Dis. **13**:572, 1886.

20. Frohmaier, G.: Ueber progressive Muskelatrophie, Deutsche med. Wchnschr. **12**:394 and 410, 1886.

21. Lorenz, H.: Die Muskelerkrankungen, Vienna, Alfred Holder, 1904.

22. Foix, C., and Nicolesco, I.: Lesions du système nerveux central dans la maladie de Thomsen et les myopathies, Ann. d'anat. path. **1**:299, 1924.

23. Poinso, R., and Poursines, Y.: Considérations anatomiques et pathogèniques sur les myopathies (à propos d'un cas personnel de myopathie à type Leyden-Moebius avec granulie cancéreuse terminale), Rev. franç. d'endocrinol. **12**:357, 1934.

24. Ballet, G., and Laignel-Lavastine: Myopathie ancienne avec disparition d'un grand nombre des cellules radiculaires anterieures, Encéphale **3**:229, 1908.

EXPERIENCES WITH INTRAMEDULLARY TRACTOTOMY

II. IMMEDIATE AND LATE NEUROLOGIC COMPLICATIONS

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In 1938 Sjöqvist,[1] Stockholm, Sweden, described a new operative procedure for the relief of facial pain which was based on, and took advantage of, the peculiar anatomic and physiologic features of the intramedullary fibers of the trigeminal nerve. Briefly, the method involves the making of an incision into the lateral aspect of the medulla oblongata, about 3.5 mm. deep and 3.5 mm. long, and so placed as to transect the descending tract and spinal nucleus of the trigeminal nerve. In this way, half of the face is rendered analgetic and thermanesthetic, since the fibers for pain and temperature sense course in the descending tract. Tactile sensation, however, is not grossly disturbed because practically all the fibers conveying touch sensation terminate immediately in the main sensory nucleus of the trigeminal nerve, after entry of the nerve into the brain stem.

The introduction into neurosurgical practice of such an unusual innovation as an operation on the medulla oblongata carries with it the obligation of describing and appraising the neurologic sequels which might be imagined to follow an incision into so vulnerable a structure. Little information, however, has been published concerning these complications, possibly because attention and interest have been focused on the sensory alterations produced by the operation and on the clinical results obtained.

In his monograph,[2] which included the case histories of 9 patients on whom intramedullary tractotomy was performed, Sjöqvist stated: "No definite signs indicating a lesion to the dorsal nuclei were seen in the postoperative course of any case." Again, later, "No symptoms of dizziness or hemiataxia which might be interpreted as signs of lesion to the restiform body were seen." Perusal of his protocols, however, offers evidence to the contrary. In his case 9, he remarked that after operation the patient's gait "was more markedly staggering than upon admission." In his case 4, the patient "noticed some feeling of numbness of . . . the right side of his body (except the arm)," which Sjöqvist was inclined to believe was caused by the operation.

Other investigators have had similar experiences but, again, have glossed over, or at least have failed to emphasize, these neurologic complications. In 1 of the 3 patients operated on by Rowbottom,[3] there were "a wild ataxia of the homolateral arm" and mild ataxia of the leg. These sequelae were said to have dis-

From the Neurosurgical Service and Laboratory of the Hospital of the University of Pennsylvania.

1. Sjöqvist, O.: Eine neue Operationsmethode bei Trigeminusneuralgie; Durchschneidung des Tractus spinalis trigemini, Zentralbl. f. Neurochir. **2**:274, 1938.

2. Sjöqvist, O.: Studies on Pain Conduction in the Trigeminal Nerve: A Contribution to the Surgical Treatment of Facial Pain, Acta psychiat. et neurol., 1938, supp. 17, p. 1.

3. Rowbottom, G. F.: Treatment of Pain in the Face by Intramedullary Tractotomy, Brit. M. J. **2**:1073, 1938.

appeared in three days. In a case in which Jackson operated but which Smyth[4] reported, no disturbances appeared to follow operation immediately. However, when the patient was out of bed, two weeks later, pronounced disturbances in gait were observed. It was not stated whether or when these disappeared. On the other hand, Jackson and Ironside[5] stated that there were no postoperative neurologic difficulties in the case in which they operated. Walker,[6] with experience in 2 cases, briefly stated that the postoperative course was uneventful.

We[7] previously reported in detail the nature of the sensory alterations produced, and Grant, Groff and Lewy[8] described the clinical results obtained by the procedure. In this communication, we wish to give an account of the neurologic complications observed in a series of 19 cases after tractotomy. Although operation was performed in 24 cases, our notes on a number of early cases were regrettably brief, and in a few instances no notes were recorded. Our failure at the beginning to sharpen our observations on the neurologic complications following tractotomy was due to several circumstances. First, although certain disturbances were obvious, little concern was given them and no description made in the records, partly because it was assumed that they would be transitory and partly because our interest was captured by the sensory alterations in the face. Vigorous attempts at neurologic examination were discouraged by the presence of large cerebellar dressings, which hindered cooperation and made the subjects poor witnesses. Again, in some instances, by the time the patient was out of bed the worst of the neurologic disturbances had disappeared and the opportunity to study them had passed.

It was not long, however, before it became evident that the neurologic complications were neither negligible nor always transitory. The conclusion seemed inescapable that if the operation was to compete with other, well tested procedures, the technic would have to be so modified as to eliminate the neurologic sequels. In a previous article[9] we outlined certain anatomic objections to the original operative description of Sjöqvist and, in turn, recommended a modification in the placing of the incision which we believe renders the operation less likely to cause neurologic complications. In brief, this modification consists in placing the incision about 12 mm. more caudally in the medulla, so that injury to the restiform body and the main and/or the lateral cuneate nucleus is avoided (fig. 1). It is admitted that in some of our earlier cases, in which the procedure described by Sjöqvist was followed, the medullary incision was inaccurately placed. Such inaccuracies, however, are inherent in a technic in which the incision must be placed so close to important structures that an error of only 1 or 2 mm. results in injury to them.

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4. Smyth, G. E.: The Systemization and Central Connections of the Spinal Tract and Nucleus of the Trigeminal Nerve, Brain **62**:41, 1939.

5. Jackson, H., and Ironside, R.: Left Trigeminal Pain Treated by Sjöqvist's Medullary Trigeminal Tractotomy, Proc. Roy. Soc. Med. **32**:219, 1939.

6. Walker, E. A.: Anatomy, Physiology and Surgical Considerations of the Spinal Tract of the Trigeminal Nerve, J. Neurophysiol. **2**:234, 1939.

7. (*a*) Weinberger, L. M., and Grant, F. C.: Experiences with Intramedullary Tractotomy: III. Studies in Sensation, Arch. Neurol. & Psychiat. **48**:355 (Sept.) 1942. (*b*) Grant, F. C., and Weinberger, L. M.: Experiences with Intramedullary Tractotomy: I. Relief of Facial Pain and Summary of Operative Reseults, Arch. Surg. **42**:681 (April) 1941.

8. Grant, F. C.; Groff, R. A., and Lewy, F. H.: Section of the Descending Spinal Root of the Fifth Cranial Nerve, Arch. Neurol. & Psychiat. **43**:498 (March) 1940.

9. Grant, F. C., and Weinberger, L. M.: Experiences with Intramedullary Tractotomy: IV. Surgery of the Brain Stem and Its Operative Complications, Surg., Gynec. & Obst. **72**:747, 1941.

Because of the modification in operative technic, our series of cases falls into two periods: cases in which operation was performed before, and those in which it was performed after, the adoption of the surgical modification. Of the 24 cases in which operation was carried out, the notes in only 19 are sufficiently detailed for report, for reasons already mentioned.

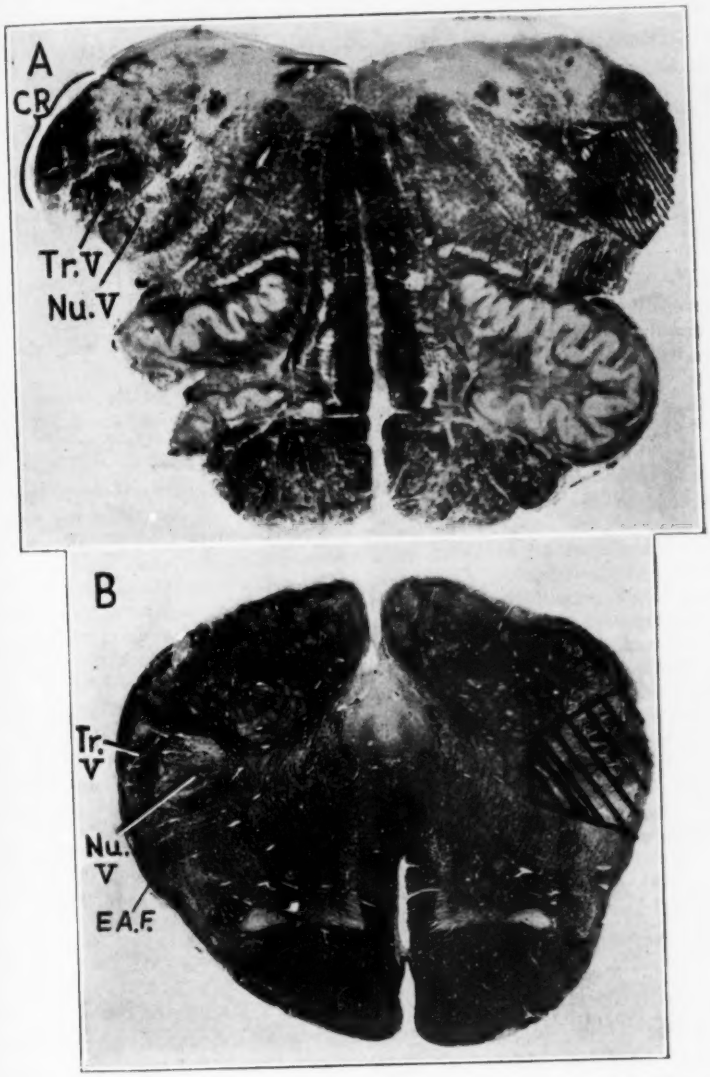

Fig. 1.—*A*, Transverse section of the medulla at the level of the middle of the inferior olive, showing degeneration of the spinal tract of the fifth nerve; Marchi stain (after Sjöqvist [2] [fig. 32]). The proposed incision, indicated by the shaded area, involves almost the lower half of the corpus restiforme (C. R.).

B, cross section through the medulla 4 to 5 mm. below the obex and about 2 mm. caudal to the olive. The extent of the modified incision is shown by the shaded area. At this level the descending tract of the fifth nerve (*Tr. V*) is most superficial and is covered only by a thin band of external arcuate fibers (*E. A. F.*). The spinal nucleus of the fifth nerve (*Nu. V*) is also shown to be fairly superficial.

Since autopsy studies are lacking in all but 1 of the cases to be reported, no precise correlation can be offered between the clinical disturbances observed and the nerve structures injured. However, reflection on the region of the medulla concerned permits some general speculation with regard to the structures that may have been involved. Further we cannot go; for this reason, our presentation of the cases will be purely reportorial. Inasmuch as intramedullary tractotomy is a new and still experimental operation, it seems worth while to recount as fully as possible our experiences with it, just as they occurred, and to leave for the moment the question of anatomicoclinical correlations until more autopsy material is available. The cases will be presented in the chronologic order of operation.

TRACTOTOMIES PERFORMED WITH THE ROSTRALLY PLACED INCISION OF SJÖQVIST

CASE 1.—J. E., a man aged 74, had major trigeminal neuralgia affecting the second and third divisions of the right fifth nerve. Intramedullary tractotomy was performed in April 1939.

There was conspicuous incoordination of the right arm immediately after operation. On the tenth postoperative day, when the patient was taken out of bed, he was unable to walk because of pronounced staggering and falling to the right. At this time there was still moderate incoordination of the right arm.

For several weeks after operation, and after his discharge from the hospital, the patient stated that his gait was staggering. It slowly improved over the course of several months. He also noticed that his handwriting was jerky and irregular for several months after operation.

He was seen in the follow-up clinic in January 1940, nine months after operation. He reported that he was able to walk about the house without difficulty, but that when he ventured on the street, he required the use of a cane because of mild unsteadiness of gait. Examination disclosed that he walked with a widened base and that there was a moderate degree of ataxia. He used his right leg awkwardly and was unable to walk a straight line, always stepping to the right. He staggered on attempting a quick turn. The upper portion of his body was inclined to the right in a way reminiscent of a man leaning into a wind. His right leg showed only slight ataxia in the heel to knee test, much less severe than one would expect from his disturbance in gait. There was no trace of incoordination in his right arm. His handwriting was excellent. There was no disturbance of sensation in his extremities. Power was intact in all extremities, and all the deep reflexes were normal.

He was again seen in July, fourteen months after operation. He reported that he was walking much better and had discarded his cane. He was conscious of tending to veer toward the right on walking and was aware that he tended to "throw" his right leg. It was sometimes necessary for him to "catch himself" when arising quickly from a chair or making a quick turn. On examination, it was noted that his trunk was still slightly inclined to the right. When he attempted to walk a straight line, he occasionally lurched to the right. He was able to ascend stairs rapidly and to descend them with ease. Except for these minor difficulties, his neurologic status was normal.

All three divisions of the trigeminal distribution were analgetic, and his neuralgia was completely relieved.

While the worst of the neurologic disturbances lasted only a few weeks, the patient was considerably inconvenienced for several months. We are inclined to believe that the restiform body was injured by the medullary incision.

CASE 2.—H. W., a woman aged 65, had intractable pain due to a carcinoma of the left maxillary sinus. Intramedullary tractotomy was performed in April 1939.

Unfortunately, this patient was not examined during her immediate postoperative course. However, it was noted that when she was taken out of bed, on the eighth postoperative day, there was great unsteadiness of gait and she staggered to the left. She subsequently stated that all disturbances in walking passed away two or three weeks after operation.

She was seen in June, two months after operation, at which time she had no complaints referable to the nervous system. Except for slight swaying when she was in the Romberg position and a fine nystagmus when she looked to the left, her neurologic condition was entirely normal. She was completely free of pain, and all three divisions of the territory of the left trigeminal nerve were analgetic.

The patient was one of the few who apparently escaped any serious injury of the neighboring structures, even though the medullary incision was made high in the medulla. Had our experience been limited to 1 or 2 such cases, we should also have received the impression that the procedure had few potential hazards.

CASE 3.—W. S., a man aged 53, had a questionably malignant tumor of the left maxillary sinus, which caused severe pain. Left intramedullary tractotomy was performed in April 1939.

The only note on the hospital record stated that after operation there were a moderate degree of incoordination of the left arm and moderate disturbance of gait, the patient staggering to the left. When he was seen a year later, he gave the following information: He had been "wobbly" on his feet for about a month after discharge. The clumsiness of his left hand had also disappeared in a few weeks. For several weeks after discharge he experienced numbness and tingling in the left hand and fingers. He had considerable weakness of his left hand and arm for five or six months after operation. He returned to work seven months after operation, when he was well except for slight weakness of his left arm.

He was seen in the follow-up clinic twelve months after operation, at which time he had no neurologic complaints. His neurologic condition was normal. He was entirely free of pain, the tumor having been eradicated. Sensory examination of the face showed only slight hypalgesia in the first division of the trigeminal nerve, although immediately after operation there had been analgesia in the first division and pronounced hypalgesia in the lower two divisions of distribution in the face.

This patient had sufficient neurologic disability so that he was not able to return to work for six months because of weakness of his arm. It is our impression that the alleged weakness was due to interference with postural sensation rather than to injury of the motor pathways. This inference is based on his complaint of numbness and tingling in the left hand—evidence of injury to the cuneate nucleus. This phenomenon will be more clearly illustrated in subsequent case reports.

CASE 4.—A. P., a woman aged 51, had a malignant tumor of the parotid gland. Left intramedullary tractotomy was performed in April 1939.

Immediately after operation members of the staff noted marked incoordination of the left arm. The performance of rapid alternate movements in the arm was noticeably impaired. This disturbance improved gradually after the patient's discharge from the hospital and eventually disappeared, although it is not known how long this required. A letter received from the patient about six months after operation, and written by herself, showed an even, regular script.

After operation there were analgesia in all three divisions of the trigeminal nerve and complete relief of pain.

Our information is fragmentary, but it appears that the patient suffered little inconvenience from the operation. Unfortunately, she was not carefully examined after operation.

CASE 5.—M. T., a woman aged 63, had major trigeminal neuralgia involving the third division of the left nerve. Intramedullary tractotomy was performed in May 1939.

Immediately after operation the left arm showed marked incoordination, which persisted during the patient's stay in bed, although it slowly diminished. There was no loss of power in the left extremities and no disturbance of sensation in the left arm. When the patient was placed on her feet, on the seventh postoperative day, she was unable to walk unsupported because of ataxia and falling to the left. Her gait, however, rapidly improved, and she was able to walk unsupported at the end of the second postoperative week, although her gait was slow and guarded. At the time of discharge, on the nineteenth postoperative day, there was no longer any incoordination in her arm. The disturbances in gait, as we were subsequently informed, largely disappeared within two or three weeks after operation.

The patient was seen in December, six months after operation. At that time the only difficulty she noticed was a tendency to lurch to the left when she arose quickly from a chair or made a sudden turn. The results of neurologic examination were entirely normal except that the tendency to lurch on quick movement was confirmed.

She was again seen in the follow-up clinic in July 1940, thirteen months after operation. There was no neurologic complaint of any kind, nor did examination disclose any neurologic disturbances. The left side of her face, which had been completely analgetic after operation, had now regained sensation completely. There was no return of the neuralgia, although she occasionally experienced slight quivering and burning sensations at the angle of the mouth.

Although the incision in this case was also made high in the medulla, the subsequent neurologic complications were mild and lasted but a few weeks. Their brief duration may have been due, however, to the fact that the incision was not made deep enough to produce lasting analgesia. Had this been done, it is possible that the neurologic complications would have been more severe. Our reason for saying this will be stated later.

CASE 6.—R. A., a man aged 49, had symptomatic trigeminal neuralgia involving the second division of the left nerve, apparently due to multiple sclerosis. Neurologic examination before operation showed moderate ataxia of gait and moderate incoordination of both upper extremities, tremor of the head, nystagmus, slight spasticity of the legs, hyperreflexia and a Babinski sign on the left side. Left intramedullary tractotomy was performed in June 1939.

After operation there was a decided increase in the ataxia of the extremities on the left side. The patient was able to walk with a little support. No other notes were made during the immediate postoperative period. There were analgesia of the lower two divisions of distribution of the trigeminal nerve in the face and relief from neuralgic pain.

The patient was seen in September, two and one-half months after operation. He stated that since operation his gait had been so unsteady that people thought him drunk. Examination showed severe difficulty in gait, with staggering to the left, but he could walk unsupported. Although there was considerable ataxia of all four extremities, the left arm and the left leg were more affected than the right. Difficulty in performing rapid alternate movements was especially noticeable in the left arm. Sensation was intact in all extremities.

The patient was seen again in May 1940, eleven months after operation. He still complained of difficulty in gait and required support to walk. Although he was ataxic in all extremities, the left arm and leg were more affected than the right. The sensory defect produced in his face by operation had largely disappeared, and he again experienced attacks of trigeminal neuralgia. He was readmitted to the hospital, and a retrogasserian neurectomy was performed.

It is difficult to pass judgment on the neurologic effects of tractotomy in this case because of the associated diffuse disease of the central nervous system. It may be, of course, that the increase in symptoms represented merely the usual progression of the disease. On the other hand, the patient was more incoordinate after the operation than before; so we feel that the operation must be held responsible for part, if not for all, of the increase in symptoms and signs. It must not be overlooked, however, that neurologic compensation is less likely to occur in an already severely damaged nervous system, and this may explain the patient's protracted difficulties from our incision, even though it was not deep enough adequately to relieve pain.

CASE 7.—F. W., a man aged 65, had a painful carcinoma of the right cheek. Right intramedullary tractotomy was performed in August 1939.

On the second postoperative day a confusional psychosis developed, and the patient was entirely inaccessible to examination. He was taken out of bed on the tenth postoperative day and placed on his feet. He could not stand or walk without support and constantly fell to the right. The pronounced incoordination of gait was still present on the thirteenth day, when it became necessary to remove him to an institution. He remained psychotic until his death, two months later, and we were unable to obtain any further information concerning his neurologic status.

Although we were not able to examine this patient, it was our impression that there was considerable neurologic disability, most evident in disturbances of gait and equilibrium.

CASE 8.—E. V. B., a man aged 56, had major trigeminal neuralgia affecting the second division of the right nerve. Right intramedullary tractotomy was performed in August 1939.

Immediately after operation incoordination was marked in the right arm and present, although mild, in the right leg. When he was placed on his feet, on the eleventh postoperative day, there were considerable staggering and falling to the right. At the time of discharge from the hospital, on the sixteenth postoperative day, he still required support in walking because of staggering. He subsequently told us that there was a decided stagger in his gait for several weeks after discharge and that because of it he was not able to walk straight. His family noted that he tended to incline his trunk to the right side and that he veered to the right when

walking. His right arm also remained awkward and clumsy for several weeks after his return home. He had not noted any unusual sensations in his hand.

The patient was seen in the follow-up clinic in January 1940, five months after operation. He admitted that there was still slight disturbance in gait, which was not noticeable under ordinary circumstances. He had gone back to work as a carpenter but noticed that he frequently missed nails that he was hammering and that his arm felt a little clumsy when he was using tools. The latter complaint was largely subjective, since his work did not suffer because of it.

Examination showed little neurologic disturbance. He walked with a slightly widened base and lurched occasionally to the right when making a sudden turn on command or when walking fast. With his eyes open, he walked in a perfectly straight line but tended to veer to the right with his eyes shut. In spite of the alleged clumsiness of his right arm, clinical tests failed to show any evidence of incoordination. The rest of the neurologic examination also gave normal results.

The patient was seen again in the follow-up clinic in July, eleven months after operation. He still noticed that when he walked too fast or too far his gait became a little unsteady and he tended to veer to the right. His ability to use hammer and nails had improved, and he stated that he only occasionally missed. On examination he made an occasional sideward step to catch himself when he was walking with his eyes closed. Other than this minor defect, the results of neurologic examination were normal. Sensory examination of the face showed analgesia in all three divisions of the fifth nerve, and there was complete relief of pain.

The neurologic complications observed in this case were probably due to associated injury of the restiform body. The patient was largely incapacitated for two or three weeks after operation but made an essentially complete recovery within four to six weeks after operation.

CASE 9.—R. J., a man aged 45, had carcinoma of the tongue and severe, intractable pain. Left intramedullary tractotomy was performed in December 1939. In addition, the glossopharyngeal nerve and the posterior roots of the upper three cervical nerves were sectioned.

Examination on the second postoperative day revealed pronounced incoordination of the left arm when the eyes were closed and a somewhat less severe disturbance with the eyes open. Investigation showed that, in addition to the cerebellar component, there was a considerable degree of ataxia in the left arm referable to the posterior column. Postural sensation was almost absent in the fingers and was decreased as high as the elbow. There were pseudoathetotic movements of the fingers of the left hand. Power was decreased almost 50 per cent in the left arm and the left hand grip as compared with that in the right. The deep reflexes in the left arm were slightly decreased as compared with those in the right arm. Power was intact in the lower extremities. There was slight ataxia in the left leg in the heel to knee test. The patient complained of numbness and tingling in the fingers of the left hand. In spite of the impairment in postural sensation, vibratory perception in the fingers of the left hand was equal to that in the fingers of the right hand. There was no loss of cutaneous sensation.

During the subsequent postoperative days the incoordination of the left arm lessened and power slowly returned. Nine days after operation, however, there was still considerable impairment of postural sensation in the hand and fingers on the left side. The hand was numb and tingling. At this point examination revealed no disturbances in stereognosis, although objects were handled clumsily. When the patient was placed on his feet, he was unable to stand or take steps unsupported, but staggered and fell to the left side. He seemed utterly unable to maintain his body balance. Although there was still incoordination of the left arm, little or none was elicitable in the left leg by ordinary tests; it seemed, therefore, that the disturbances in equilibrium could hardly be accounted for on the basis of involvement of the cerebellar pathways. The phenomenon appeared to be vestibular.

When he was discharged, on the fourteenth postoperative day, he was still unable to walk without assistance, although the ataxia was less severe. The disturbances in the left arm were still present, but were greatly improved over his immediate postoperative status.

The patient lived two and one-half months after operation. A letter received from his wife just before his death stated that he was able to walk but staggered to the left, that his left arm and hand were clumsy and that he still experienced numbness in the left hand.

After operation there were analgesia in all three divisions of the trigeminal nerve and analgesia and anesthesia of the pharynx and the left side of the neck. The patient was free

of pain until shortly before he died, at which time pain developed in the top of his head, doubtlessly as a result of metastases.

From the nature of the neurologic disturbances, it is likely that the cuneate nuclei, as well as the restiform body, were injured by the medullary incision although the production of analgesia of the face indicates that the incision was placed with some degree of accuracy. The peculiar disequilibrium, which appeared to be vestibular in nature, raised the suspicion that the vestibulospinal tract was injured. This case illustrates the potential hazards of an incision placed in such close proximity to important nuclei and tracts. Had the patient lived longer, there would doubtless have been considerable improvement in his neurologic status; he was, nevertheless, seriously handicapped for two and one-half months.

Case 10.—C. K., a man aged 55, had a carcinoma of the tongue which was infiltrating the mandible and causing severe, intractable pain. Right intramedullary tractotomy was performed in January 1940.

Twenty-four hours after operation examination disclosed wild incoordination of the right hand, the arm being useless for almost any task. The patient complained of feelings of numbness and tingling in his right hand and fingers. There were conspicuous pseudoathetoid movements of the outstretched hand and fingers. Postural sensation was almost absent in the fingers and considerably impaired at the right wrist. There was definite dysstereognosis in the right hand, the patient being unable to identify simple objects, although he could recognize some of their attributes, such as roundness or angularity. He could not differentiate cloth from paper or roughness from smoothness. In addition, he could not properly estimate the weight of objects placed in his right hand. He consistently stated that the object in his right hand was lighter than that in the left, when in reality it was considerably heavier. Vibratory sensation, as tested with the clinical tuning fork (128 double vibrations per second), was as well perceived in the hand and fingers on the right side as in those on the left. There was mild weakness of the right arm and the right hand grip. The right leg showed only slight incoordination in the heel to knee test. Cutaneous sensation was intact in both right extremities. Nystagmus was not present.

On the third postoperative day the status was much the same except that the signs had all diminished in intensity. The weakness of the grip in the right hand seemed more evident, however. Sensory examination of the face disclosed only slight hypalgesia in the lower two divisions of the fifth nerve.

On the seventh postoperative day there was still pronounced incoordination of the right arm, which seemed to be about equally compounded of cerebellar dyssynergia and posterior column ataxia. Power was still noticeably reduced in the right hand and the right arm. The deep tendon reflexes in the right arm were less active than those in the left. Postural sensation was still greatly impaired in the fingers of the right hand. Vibratory sensation was intact. There was still dysstereognosis in the right hand. The incoordination of the right leg had almost disappeared. His neurologic condition slowly improved, although his general condition was poor. He was discharged on the sixteenth postoperative day.

The patient was examined in his home twenty-four days after operation, and two weeks before his sudden death from laryngeal edema. At the time of examination he was found sitting in an easy chair. He had not been able to feed himself because of the incoordination in his arm. He was able to stand unsupported with his legs spread wide apart but promptly fell to the right on his attempting the Romberg maneuver. When he fell, he made no movements of postural adjustment to "catch himself," but fell en masse, like a statue. When he was supported and encouraged to take steps, his trunk inclined far to the right. The tilting of the body, the tendency to fall and the pronounced staggering reminded one of a severe vestibular disturbance. The extreme disturbance of equilibrium and the trunkal ataxia were entirely out of proportion to the slight evidence of incoordination in the right leg when the patient was tested lying down. On attempting to walk, however, he handled his right leg awkwardly. There were decided "drifting" of his right arm when it was held outstretched and constant pseudoathetoid movements of the fingers, of which he was not aware. The incoordination of the right arm was still pronounced, but considerably less so than when he was discharged from the hospital. The impairment of postural sensation in the fingers and hand on the right side was about the same as at the time of discharge, being almost complete in the fingers. The dysstereognosis was still present, the patient being able to do no more than recognize certain qualities of objects placed in his hand. Vibratory perception and cutaneous sensations were intact in the right hand. Two point discrimination

was slightly impaired. He was still unable to judge the relative weights of objects with his right hand. There was no alteration of tone in the right arm, but the weakness of the hand grip was still easily evident.

It was the examiner's opinion that there had been moderate improvement in the incoordination of the right arm but that the impairment of postural sensation in the right hand and the disturbance of gait had shown little or no improvement since the patient's discharge from the hospital. There was slight hypalgesia in the lower two trigeminal divisions of the face. This had been sufficient to ameliorate his pain, but not to relieve it entirely.

In this case, and in case 9, the evidences of neurologic injury were most severe. One wonders how long it would have taken for complete recovery to have occurred. Apparently, neurologic compensation takes place more quickly when the injury is confined to the restiform body than when both it and the cuneate nuclei, and possibly the vestibulospinal pathways, are injured. Moreover, the disturbances in postural sensation and in equilibrium appear to persist longer than does the cerebellar dyssynergia.

It was realized at the operating table that the incision had been extended too far dorsally and that the restiform body and the cuneate tubercle had been partly cut across. It was thought at the time, although proved wrong later, that the incision had been deep enough to sever the descending tract of the trigeminal nerve. Although permission for autopsy was not granted, and therefore the exact extent of the lesion could not be verified, it is believed that the neurologic signs witnessed represented the combined syndrome of the restiform body and the cuneate tubercle. The vestibulospinal tract was possibly also injured. The interesting and important physiologic information derivable from instances of this kind will be discussed in a subsequent communication.

TRACTOTOMIES PERFORMED WITH THE MODIFIED INCISION

The opportunity to perform autopsy in a case in January 1940 in which operation had been done in May 1939 furnished us with a clue that led to modification of the technic. When the brain stem was sectioned, it was observed that the medullary incision had been made 8 mm. below the level of the obex, whereas we had previously been accustomed to make it several millimeters above the level of the obex (fig. 2). This fact had not been recognized at the operating table.

However, as the subsequent history (case 11) shows, the patient had complete analgesia in all three divisions of his face. This observation suggested that, contrary to general opinion, all divisions of the trigeminal nerve are represented in the descending tract at a low level in the medulla. It had been thought that the fibers from the mandibular and maxillary divisions terminated in the spinal nucleus of the trigeminal nerve at a rather high level in the medulla, which may have accounted for Sjöqvist's placing the incision in the descending tract at a point opposite the open fourth ventricle. With this new information, it was apparent that the incision could be made routinely at a more caudal level of the medulla, with, at the same time, much less chance of injuring the restiform body. Because the lower portion of the medulla could be visualized more clearly, there was also less likelihood of injury to the posterior column or the cuneate tubercle. The subsequent 8 cases, cases 12 to 19, illustrate the results of the modification.

CASE 11.—H. H., a man aged 55, had carcinoma of the right mandible. Right intramedullary tractotomy combined with section of the glossopharyngeal nerve and the posterior roots of the upper three cervical nerves was performed in May 1939. There was no information on the immediate postoperative course, but the note at the time of discharge stated briefly that there were pronounced staggering and falling to the right but no incoordination of the right arm.

The patient was examined at another hospital in January 1940, eight months after operation and three weeks before his death. He had undergone resection of the mandible several

weeks previously, as a result of which he could not speak; the neurologic history in the interval could not, therefore, be obtained. The patient was able to stand and walk unsupported, although his base was widened and he occasionally lurched to the right. The upper part of his trunk was slightly inclined to the right. He fell to the right on performing the Romberg maneuver. There was no evidence of weakness or of incoordination in his right arm. There was slight ataxia in the right leg in the heel to knee test. All the reflexes were equal on the two sides.

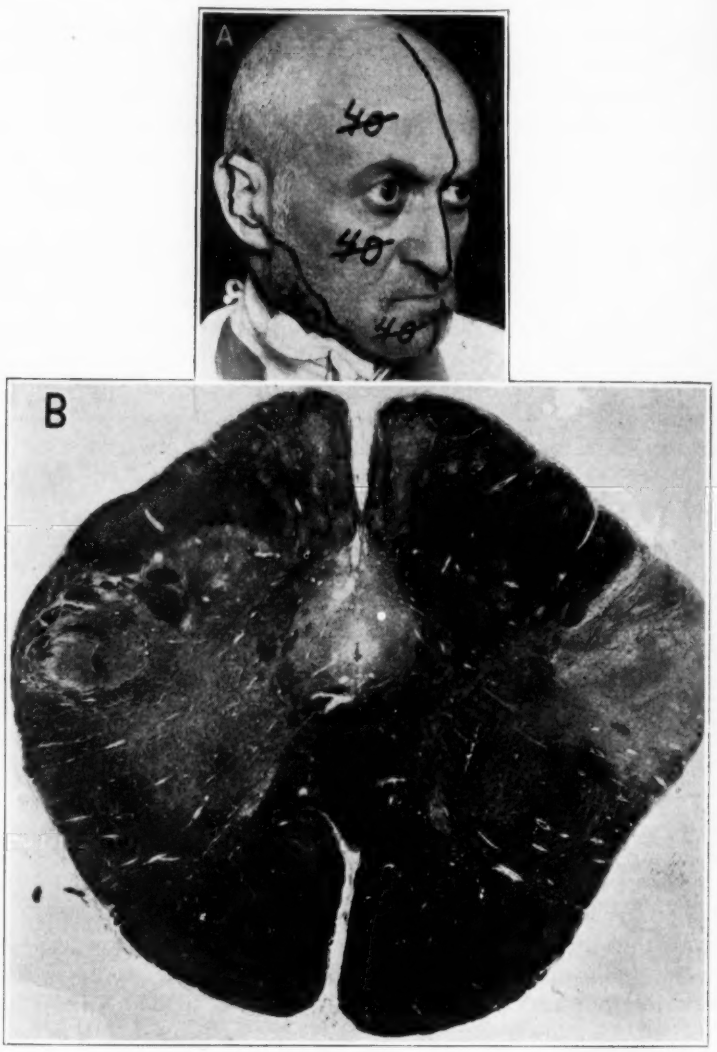

Fig. 2. (case 11).—*A,* postoperative photograph of the patient, showing areas of sensory loss. The numeral *40* with the line drawn through it means that more than 40 Gm. of pressure with a Head algesiometer failed to provoke pain sensation—in other words, analgesia.

B, section through the medulla 7 to 8 mm. below the obex. The demyelinated, wedge-shaped area of destruction represents the site of the surgical incision (tractotomy), which encompasses the descending tract and the spinal nucleus of the trigeminal nerve. Judging from the complete analgesia of the right half of the face, all three divisions of the trigeminal nerve are represented in the descending tract at this level of the medulla.

Sensory tests disclosed hypalgesia of the left side of the body and extremities, with preservation of touch sensation. The right side of his face was analgetic, and the pharynx

and the right side of his neck were anesthetic and analgetic. The analgesia of his face and neck was so profound that the resection of the mandible had been accomplished without the use of an anesthetic agent.

The patient's extreme cachexia and weakness enhanced the neurologic signs, which, however, were not extreme. As a matter of fact, it is difficult to account for their presence, since sections of the brain stem secured at autopsy (fig. 2) showed that neither the restiform body nor the cuneate nucleus had been injured. This was the only case in our series in which a crossed sensory syndrome (Wallenberg syndrome) occurred as a complication. Possibly the result indicates that the incision was placed a trifle too deep and ventral.

Schwartz and O'Leary [10] recently reported on an experimental operation in which they transected the lateral spinothalamic tract in the medulla oblongata for the relief of pain in the upper portion of the arm and the upper part of the chest, areas which are difficult to render analgetic by the classic chordotomy. They succeeded in producing hypalgesia of these regions by incising the medulla to a depth of 6 mm. at a point just dorsal to the caudal end of the inferior olive. The concept of section of the spinothalamic tract in the medulla for the relief of pain about the shoulder and neck had occurred to us in 1939, as a result of our experiences with tractotomy, but a suitable case did not present itself. However, the feasibility of the procedure is confirmed by our experience in a case in which the lateral spinothalamic tract was inadvertently severed at operation, in 1939.

As has been mentioned, the significant observation derived from this case is that analgesia of the face may be produced by an incision more caudal than had heretofore been made. In the next case to be described the incision was deliberately placed more caudally than in the earlier cases, although not as far as that in case 11.

CASE 12.—J. S., a minister aged 58, had severe major trigeminal neuralgia involving the first and second divisions of the left nerve. Left intramedullary tractotomy was performed in March 1940.

The patient was carefully examined eight hours after operation. There was wild incoordination of the left arm, so severe that he struck himself in the face on attempting to touch his nose. He complained of numbness and tingling in the left hand and fingers. Postural sensation was absent in the fingers of the left hand and was greatly impaired at the wrist. Vibratory perception was intact, however. Stereognosis was not disturbed in the left hand. Power seemed to be equal in the two upper extremities. There was moderate incoordination of the left leg.

The patient was again examined forty-eight hours after operation. There was rotatory nystagmus on his looking to the right. The incoordination of the left arm was pronounced, but was less severe than immediately after operation. The incoordination was due as much to loss of postural sensation in the hand as to the cerebellar components. He still complained of numbness and tingling in the left hand.

On the fifth postoperative day the incoordination of the left arm was much decreased. He was able to recognize the position of his fingers in space when the stimulus was strong. Power was equal in his upper extremities. There were no disturbances in cutaneous sensation. The left leg showed mild ataxia in the heel to knee test. The nystagmus had disappeared.

The patient was taken out of bed on the sixth postoperative day. He was entirely unable either to stand or to walk because of severe disturbance of equilibrium. He spread his legs far apart in an effort to stand but promptly fell over to the left. There were no reactions of defense in order to balance himself, and he fell over like a toppling statue.

On the seventh postoperative day the patient was able to stand unsupported with his legs straddled, but fell over on attempting to take a step. The upper part of his body tilted far over to the left. The inclination of the trunk, the severe disturbance of equilibrium and the inability to make defensive balancing motions, along with the immediate falling to the left

10. Schwartz, H. G., and O'Leary, J. L.: Section of the Spino-Thalamic Tract in the Medulla with Observations on the Pathways for Pain, Surgery **9**:183, 1941.

when he attempted to walk, seemed to represent a severe vestibular disturbance. The left leg was handled clumsily but showed only slight incoordination in the heel to knee test, far less than one would expect from the disturbance of gait. The left arm showed now only a mild degree of incoordination, and the patient could use it for simple tasks. He complained of tingling in the left hand, but the sense of numbness had disappeared. The disturbance in postural sensation in the fingers had largely disappeared, although it was still present to a slight degree.

On the eighth postoperative day the the patient was able to take a few steps by carefully watching his feet but fell over on looking away. His trunk was carried strongly inclined to the left. He stood with his legs wide apart and fell over on bringing them together. The incoordination of his left arm was slight, and there was only mild impairment in the performance of rapid alternate movements. A slight rebound phenomenon was elicitable in the left arm. In the left leg there was just a trace of ataxia when he performed the heel to knee test. The disturbance of postural sensation in the left hand had disappeared, although he still complained of a continuous tingling sensation. The striking observation was the marked disturbance in equilibrium and body posture, as compared with the slight evidences of incoordination when the extremities were tested separately.

On the tenth postoperative day the patient was able to walk the length of the hospital room unsupported, but he moved with short, shuffling and guarded steps. He frequently staggered and lurched to the left and completely lost his balance on making a turn. His inability to make the necessary postural adjustments to rescue himself from falling was still conspicuous. There was no longer any evidence of dysmetria or dyssynergia in the left arm, as judged by the usual tests. Past pointing was not present.

On the twelfth postoperative day he was able to walk fairly well unassisted, although he staggered to the left every six or eight steps. His gait was shuffling and guarded; when he was encouraged to take long steps, his gait became unsteady, he would cross his legs and, if not caught, would fall. He was able to stand in the Romberg position for ten or twelve seconds; then he would sway and fall over. The usual reactions of defense to threatened loss of balance were absent. He made no attempt to throw out his arms or shift his stance or center of gravity, but fell over like a statue. He stated that he did not realize he was falling until it was too late to regain balance. If his pelvis was passively tilted backward or to the left, he made no counterreflexes to regain equilibrium. Although the left arm and hand showed no neurologic abnormalities, he still complained of tingling in his fingers.

He continued to improve from day to day, and on the sixteenth postoperative day his gait and postural reactions showed only mild disturbances. He walked freely but tended to veer to the left and occasionally made a sideward step. He could not, however, walk a line or balance himself standing heel to toe. He was able to stand in the Romberg position.

The patient was discharged on the eighteenth postoperative day. At this time his gait was almost normal except that he occasionally lurched to the left. He still staggered a little on making a sudden turn. The postural reactions to his being placed off balance were still greatly impaired, although they were improved. He was able to walk up stairs easily but not down stairs, as he could not balance himself and would have plunged headlong if he had not been protected. He had a subjective feeling of insecurity in using his left hand, but the usual gross tests showed nothing abnormal.

There was analgesia of all three divisions of the trigeminal nerve on the left side of his face, with complete relief from pain.

The patient was seen in the follow-up clinic in April, just one month after operation. Except for minor difficulties, his neurologic status was normal. He walked with a slightly widened base. When he rose quickly from a chair, he lost balance and tended to stagger to the left. He walked freely and easily. He stated that his left hand was a little clumsy in handling table utensils or buttoning his clothes, but the usual tests showed nothing abnormal. There was still a deficiency in making his postural adjustments to regain equilibrium when his body was passively tilted to the left.

A letter was received from the patient in July, three months after operation. He had resumed his ministerial duties. There were several minor complaints. The tingling still persisted in his fingers but was mild. He confessed to a little awkwardness in the use of his left hand when he performed complicated movements. He had typewritten his letter, and he apologized for the many errors in it, saying that the fingers of his left hand did not hit the keys properly. When he was fatigued or when he walked too long, his gait became a little unsteady. Other than these complaints, he was vigorous and in perfect health. He was well pleased that his neuralgia had been relieved without production of numbness in his face.

Because the neurologic signs were studied more intensively in this case than in any other, one may have the impression that the postoperative neurologic complications were severe. As a matter of fact, the patient had recovered, for all practical purposes, on the thirteenth to fifteenth day after operation. However, it appears that the incision was made still too far rostrad and that the restiform body and the cuneate nuclei were injured, although not seriously so. From the experience gained in this case, it was decided to move the incision a trifle more caudally and ventrally in subsequent cases.

CASE 13.—N. E., a woman aged 47, had major trigeminal neuralgia affecting the second and third divisions of the right nerve. Right intramedullary tractotomy was performed in April 1940.

Eight hours after operation the patient was comfortable and cooperative. Slight nystagmus was present on her looking to the right. There was slight incoordination of the right arm. Power was unaffected, and the reflexes were equal on the two sides. There were no tingling sensations in the right hand, and postural and all other modalities of sensation were intact.

Twenty-four hours after operation there was just a trace of incoordination in the right arm. Alternate movements were well performed, but a slight degree of rebound phenomenon was noted in the left arm. There was no incoordination in the right leg. Stereognosis was intact. There was analgesia in all three trigeminal divisions of the face.

On the third day after operation there was no evidence of any neurologic abnormality when the patient was examined in bed. She was then placed on her feet, but she could neither stand nor walk unsupported. There was severe disturbance of equilibrium, and she was utterly unable to balance herself. On falling she made no efforts to regain her balance through the use of the usual posture reflexes. Again, the disturbances in gait and equilibrium were accompanied by complete absence of cerebellar symptoms when she was examined in bed.

On the fifth postoperative day she was able to walk a few steps unsupported, although her base was widened and she lurched to the right. She always "caught" herself, however, and did not fall. She was unable to stand in the Romberg position but fell promptly to the right.

On the seventh postoperative day her gait had so improved that she was able to walk unsupported. Her gait was slow and guarded, however, and she frequently staggered to the right. She could not walk a straight line, stand with her feet together or stand in the heel to toe position. She still was unable to make the correct postural adjustments to regain balance when her pelvis was passively tilted to the right.

Her neurologic difficulties rapidly cleared up, and she was discharged on the thirteenth postoperative day. With minor exceptions her gait and equilibrium were normal. She stated that her right leg felt a little awkward, and when she walked the right leg swung farther laterally than the left. If she was forced to walk rapidly, she tended to stagger to the right. With her eyes closed she veered to the right. She was still unable to walk in a straight line.

The patient was seen in the follow-up clinic in May 1940, one month after operation. She noted a little clumsiness of the right leg on going up or down stairs, but otherwise felt entirely well. She was taking complete care of her house. On examination, nothing abnormal could be detected until she was asked to descend stairs. Then it was noted that her right leg did not act with quite the facility of the left.

She was again examined in June, two months after operation. No neurologic signs could be observed. She was relieved of her neuralgia, and sensory examination showed analgesia in all three divisions of the trigeminal nerve.

The patient made a quick recovery and was, for all practical purposes, neurologically normal by the eighth or ninth postoperative day. This case demonstrates why a patient must be examined directly after operation if one is to observe the neurologic disturbances. If this patient had been kept in bed eight or nine days before we tested her gait, we should not have known that there was any disturbance and therefore should have thought that the complications were very mild and transient and that they were confined to the arm. By getting the patient out of bed on the third or the fourth day we were able to observe phenomena that other-

wise would have been missed. At this stage we felt that we had fairly well solved our problems concerning the placement of the incision. Further experience seemed to confirm this belief, although, as will be shown, the results were not constant.

CASE 14.—A. W., a woman aged 63, had major trigeminal neuralgia involving the third division of the left nerve. Left intramedullary tractotomy was performed in June 1940.

The patient was examined five hours after operation. There was no incoordination of the left arm. Nystagmus was not elicited. Sensation was intact in the left hand and fingers, and there were no subjective complaints. Analgesia existed in all three divisions of the trigeminal nerve.

Twenty-four hours after operation the patient was perfectly comfortable. A complete neurologic examination gave entirely normal results.

The patient was taken out of bed on the seventh postoperative day. She walked slowly and guardedly, but not more so than one would expect to see in an elderly woman who had been confined to bed for a week after a cranial operation. There were no evidences of neurologic disturbance. She was discharged on the twelfth postoperative day, with complete relief of her neuralgia and with analgesia of all three divisions of the trigeminal nerve.

This patient, who was observed intently, showed no evidence of neurologic injury after operation, a fact which we assign to the modification in technic. Although we did not examine her gait until the seventh postoperative day, its normality at that time argues against any considerable disturbance earlier in the postoperative course.

CASE 15.—R. P., a man aged 74, had carcinoma of the lower gum on the left side. Left intramedullary tractotomy was performed in June 1940.

Eight hours after operation neurologic examination showed that the left upper extremity was normal in all respects. The patient had no complaints referable to it. There seemed to be slight incoordination of the left leg, as indicated by the heel to knee test.

The patient was placed on his feet on the second day. He could stand unassisted with his legs spread apart, but fell to the left on placing his feet together or on attempting to take a step. The disturbance in equilibrium was far greater than one would expect from the results of neurologic examination with the patient in bed. The left leg was handled clumsily.

The disturbances of gait rapidly improved, and by the seventh postoperative day the patient was able to walk around the ward. His gait was guarded, and the steps were short, but this was due to his age and general weakness rather than to injury of the nervous system. On the ninth postoperative day an abscess of the left calf developed as a result of thrombophlebitis. He was not able to be out of bed again until the twenty-fifth postoperative day. At this time his gait showed no disturbance due to any neurologic disability, but because of his weakness, long hospitalization and loss of weight, it was shuffling and slow. He was discharged on the twenty-ninth postoperative day. The pain in his face was not completely relieved but was greatly improved. There was only slight hypalgesia in all three divisions of the trigeminal nerve.

We felt that by the seventh postoperative day the patient had recovered from whatever neurologic insult was present. Had he remained in bed for a week before complete neurologic examination, we should have thought that there was no neurologic impairment, since nothing was observable in the arm. The incision, obviously, was not made deep enough, since sensory tests of the face indicated that the descending tract had not been entirely transected. Although this error made the result somewhat unsatisfactory, the absence of severe or persistent neurologic signs again suggested that the major complications of the operation could be avoided by placing the incision in the descending tract 4 to 6 mm. below the obex.

CASE 16.—G. S., a man aged 49, had bilateral major trigeminal neuralgia affecting the second and third divisions on the right side and the second division on the left side. Left intramedullary tractotomy was performed in September 1940. At the same time, the sensory root of the right trigeminal nerve was sectioned in the posterior fossa.

Immediately after operation there was considerable incoordination of the left arm. The patient also complained of numbness and tingling in the left hand. There was no gross

disturbance either in postural sensation or in stereognosis. The left leg was clumsy when the patient was taken out of bed on the seventh postoperative day, and there was considerable staggering to the left. Improvement was rapid, and on his discharge the staggering was much less severe.

The patient later stated that he continued to lurch to the left side for about three months and that his left hand was awkward for about two months after operation. He was seen in the follow-up clinic in February 1941, five months after operation. He still complained of some unsteadiness of gait and the tendency to lose his balance and fall to the left. While shoveling coal, he had lost his balance and fallen, slightly injuring his knee. In addition, he stated that there was a sensation of numbness in his left forearm, which "ran down" into his thumb. His thumb constantly prickled. Examination showed slight incoordination in movements of the left arm.

He was again seen in the follow-up clinic in June, nine months after tractotomy. He stated that the tingling sensation still persisted in his left thumb, although it was much less marked. He also noticed that he frequently dropped table utensils from his left hand without realizing it until after they fell. When he did not "watch himself," he tended to stagger to the left. On examination it was noted that he used his left leg a little awkwardly and that with his eyes shut he veered and occasionally lurched to the left, although he always recovered himself. He was able to walk heel to toe with his eyes open. On descending stairs, he kept close to the wall, as he was unsteady. Except for these minor disturbances, his gait gave him no trouble. There was no evidence of incoordination in the usual tests. With his eyes closed, however, he could not place his finger accurately on the point of his nose. This appeared to represent a slight difficulty in postural sensation, but ordinary tests could not disclose any gross disturbance. He could identify all objects, as well as textures, with his left hand, but greater subjective effort and more time were required than with the right hand. Vibratory perception was intact, as were all modalities of cutaneous sensation. The left leg was slightly, but definitely, clumsy in the heel to knee test.

The right side of his face was entirely anesthetic as a result of section of the root. The left (tractotomized) side of his face was hypalgetic in the first division and moderately hypalgetic in the third division of the trigeminal nerve. In the second division there was only a slight degree of sensory loss, and this was patchy. The patient complained of attacks of "soreness" in the second division, associated with twitching sensations, which probably represented a beginning return of the trigeminal neuralgia.

In spite of precautions to place the incision at least 5 mm. below the level of the obex, there was undoubtedly some injury of the corpus restiforme and the cuneate nuclei. However, the neurologic disturbances, although fairly pronounced and persisting for several months, were not nearly as severe as those noted in some of the earlier cases. This case, again, illustrates how it is possible to injure important structures without securing adequate analgesia in the necessary trigeminal division, an example of the capricious results that are not always avoidable with tractotomy, even though great care is taken in placing the medullary incision.

Case 17.—B. Alt., a woman aged 53, had major trigeminal neuralgia involving all three divisions of the right nerve. Right intramedullary tractotomy was performed in October 1940.

The patient, unfortunately, was not examined during her early postoperative course. On the tenth day in the hospital a moderate degree of incoordination was noted in the right arm. Her gait was unsteady, and she veered to the right. She could ascend stairs without difficulty but was unable to descend them without help, as she lost her balance and fell forward. She was unable to walk in a straight line but lurched to the right.

Later, in a follow-up interview in February 1941, four months after operation, she remarked that she had been a little "wobbly" on her feet for three or four weeks after discharge, but this had cleared up entirely. During her stay in the hospital her right hand felt numb and tingled, and this had persisted, although it became less intense. She said that her right hand still felt "stupid," by which she meant that it was still a little clumsy and weak. Neurologic examination gave entirely normal results.

She was again seen in the follow-up clinic in June, eight months after operation. She still complained of a slight numbness and tingling sensation in the right thumb. She occasionally dropped articles from her right hand without being aware of it. The neurologic examination revealed nothing abnormal. There was not the slightest residual disturbance of gait.

Her trigeminal neuralgia was completely relieved, and the entire right half of her face was analgetic. She complained, however, of slight burning and aching about her right eye. This mild dysesthesia had occasionally been noted in other cases after tractotomy.[7] She was completely satisfied with the result of operation.

The mild and short-lived neurologic disturbances following tractotomy in this case were unquestionably due to the fact that the incision had been precisely placed in the descending tract, without any noteworthy injury of contiguous structures. However, as previous experience had shown, if this patient had been thoroughly examined immediately after operation, a much more severe disability might have been observed.

CASE 18.—J. Sch., a man aged 41, had major trigeminal neuralgia of the second and third divisions of the right nerve. Right intramedullary tractotomy was performed in December 1940.

On first examination, five days after operation, the patient was able to stand unsupported but staggered to the right on attempting to walk. He complained of numbness of the right hand and fingers. There was a mild degree of incoordination of the right arm. On the seventh postoperative day he was ambulatory and required no help in order to get about the ward. He still tended to stagger to the right but recovered himself.

He was seen in the follow-up clinic in May 1941, approximately five months after operation. He still staggered a little to the right when he walked, but this was readily compensated for. He complained that his right hand and forearm felt numb and tingled.

He was again seen in the follow-up clinic in June 1941, six months after operation. He stated that for about four months after operation he was annoyed by his tendency to lurch to the right when he walked, but this disturbance had practically disappeared. He still noticed that his right hand tingled slightly, but he had no difficulty in handling objects. A thorough neurologic examination revealed no abnormalities except that in walking with his eyes closed he occasionally lurched to the right, but instantly recovered himself.

Sensory examination of the face disclosed that the first and second divisions were entirely analgetic and the third division was notably hypalgetic. In spite of the analgesia in the second division, the patient complained of typical, although not severe, paroxysms of trigeminal neuralgia. There was, in addition, a definite "trigger point" on his upper lip, contact with which precipitated a paroxysm.

Although the neurologic disturbances persisted for several months, they were mild and hardly interfered with the patient's activities. As far as the neurologic aspects were concerned, the outcome in this case was satisfactory. However, the presence of a trigger point and neuralgia in an analgetic area is unique in our experience and raises the speculation whether trigeminal neuralgia may not depend partly on the presence of touch sensation. This disturbing observation, if confirmed on subsequent examinations, may raise a more serious objection to intramedullary tractotomy than the occurrence of neurologic complications.

CASE 19.—R. M., a woman aged 51, had major trigeminal neuralgia affecting the first division of the right nerve. Right intramedullary tractotomy was performed in January 1940.

Examination ten days after operation revealed no incoordination in the right arm. There were, however, definite difficulties in walking. The patient lurched and staggered to the right. She also complained of numbness over the ulnar aspect of the right hand.

One month after operation, examination in the follow-up clinic showed very minor disturbances. Her gait was slow and wide based, but there was no staggering. She still complained of a sensation of numbness of the fourth and small fingers and the ulnar aspect of the right hand.

She was seen in the follow-up clinic in June, about six months after operation. A sensation of numbness and tingling was still present in the outer two fingers of the right hand, but this was mild and only occasionally obtruded itself into consciousness. The neurologic examination was entirely normal.

The ophthalmic division of the trigeminal nerve was analgetic, the maxillary division moderately hypalgetic and the mandibular division slightly hypalgetic. There was complete relief from trigeminal neuralgia.

The neurologic disturbances were mild and transitory. This case serves as another demonstration that incisions placed lower in the medulla are less likely to produce neurologic complications. In this case the result was completely satisfactory.

COMMENT

There is plainly a discrepancy between our [11] early experience and that reported by other investigators with respect both to the incidence and to the severity of the neurologic complications following tractotomy. Several factors seem to account for this difference, one of which is simply quantitative—the number of cases in which the operation was performed. Had our experience been limited to cases 2, 4 and 5, in the early series, we should also have received the impression that neurologic complications either did not occur or were unimportant. The value of an operation, however, must be judged not only on the results obtained when the procedure is perfectly performed but on the complications when it is not done precisely, because of minor surgical errors in the placing of the incision, anatomic variations, obscuring by vessels of the surface of the medulla, edema, hemorrhage or other unforseeable factors. Therefore, the hazards inherent in an operation of this kind can be demonstrated only in large series in which the entire gamut of difficulties has been run.

In every instance we attempted, although in several we failed, to incise deeply enough to produce analgesia of the entire half of the face. While it is possible, of course, to injure contiguous structures without producing facial analgesia, if an incision is badly placed, the likelihood of injury of neighboring nuclei and tracts increases with the effort to transect completely the descending tract. This observation applies particularly when the incision is made at a level opposite the open fourth ventricle, but it may explain the statements of other surgeons who have claimed not to have seen neurologic sequels, for inspection of their protocols suggests that they did not incise quite deeply enough. In Sjöqvist's series, for instance, the neurologic sequels occurred only in cases 4 and 9, which were precisely those in which the most profound sensory defects were produced in the face. In cases 1, 2, 3, 5, 6, 7 and 8 there were no neurologic complications, but neither was complete analgesia produced in the half-face. We think it probable that his failure to secure analgesia and the lack of neurologic complications are both explainable on a common basis, namely, insufficiently deep incisions. In both of Walker's cases incisions were apparently inadequate also, since analgesia was not produced in either case. The same may be said of Rowbottom's second and third cases.

The delusion that neurologic complications do not occur may also have arisen from the fact that the patient is generally kept in bed and not examined on his feet until a week or ten days after operation. Thus, the "uneventfulness" of the postoperative course may be largely an impression gathered from tests only of the upper extremities during this period. As our experience amply demonstrated, various degrees of gait and equilibratory disturbances may exist during the early postoperative course but pass unnoticed unless the patient is examined on his feet.

The duration of the neurologic disturbances is directly related to their postoperative intensity. In only 5 of our early cases was the period of observation sufficiently long to enable us to witness the ultimate outcome; death prevented long term observations on most of the patients suffering from malignant disease. It is our impression, nevertheless, that if the patient had lived long enough, neurologic compensation would have occurred in all cases. This conclusion corresponds to

11. Sjöqvist.[2] Jackson and Ironside.[5] Walker.[6]

that of Ferraro and Barrera,[12] who experimentally, in the monkey, destroyed the restiform body and the cuneate nuclei, either separately or in combination.

Shifting of the medullary incision more caudally, as was previously described, greatly decreases the risk of producing serious or persistent neurologic complications, through injury to the restiform body and the cuneate nuclei, but the risk is by no means completely eliminated.

The procedure of tractotomy is just moving out of the experimental stage. The complications reported here must be expected in an operation of so delicate a character; indeed, their occurrence is salutary in that they force the devising of modifications to render the procedure safer and the results surer. Tractotomy has a place in the surgical treatment of facial pain because it offers certain advantages not obtained by the other, classic procedures. However, the results will probably continue to be more capricious than those obtained with the classic procedures. For this reason, the indications for intramedullary tractotomy are limited, and at present the operation is not to be considered as a routine treatment of major trigeminal neuralgia. Its widest usefulness, as we have previously indicated,[8a] is in the treatment of malignant disease about the face when it is desired to section the glossopharyngeal nerve and the posterior roots of the upper cervical nerves through the same incision.

SUMMARY

As a result of our experience with medullary tractotomy, it has been found that a section in the medulla placed from 6 to 8 mm. caudal to the lower end of the fourth ventricle (obex) will produce satisfactory analgesia of the face, with fewer neurologic sequelae than with the usual methods. That a section at this level produces anesthesia of the face indicates that all three divisions of the fifth nerve are represented in the descending root at this level.

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12. Ferraro, A., and Barrera, S. E.: Effects of Experimental Lesions of the Posterior Columns in Macacus Rhesus Monkeys, Brain **57**:307, 1934; Summary of Clinical and Anatomic Findings in the Dorsal Column System of Macacus Rhesus Monkeys, A. Research Nerv. & Ment. Dis., Proc. **15**:371, 1935; Posterior Column Fibers and Their Terminations in Macacus Rhesus, J. Comp. Neurol. **62**:507, 1935; The Effect of Lesions of the Dorsal Spinocerebellar Tract and Corpus Restiforme in the Macacus Rhesus, Brain **58**:174, 1935; The Effects of Lesions of the Dorsal Column Nuclei in the Macacus Rhesus, ibid. **59**:76, 1936; Effect of Lesions of the Juxtarestiform Body (I. A. K. Bundle) in Macacus Rhesus Monkeys, Arch. Neurol. & Psychiat. **35**:13 (Jan.) 1936.

SPINAL NECROSIS AND SOFTENING OF OBSCURE ORIGIN

NECROTIC MYELITIS VERSUS MYELOMALACIA; REVIEW OF LITERATURE AND CLINICOPATHOLOGIC CASE STUDIES

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There are numerous reports in the literature, under varying designations, concerning diseases of the spinal cord of undetermined origin, with softening or necrosis the prominent postmortem feature. The subject has been one of general confusion. No classification has been possible in the face of ignorance of etiologic factors; pathogenesis has been equally uncertain, and the interpretation of pathologic material has produced no uniformity of opinion regarding the nature of the morbid changes. Some investigators have assumed the process to be inflammatory and have applied the term "necrotic myelitis." Others have preferred "myelomalacia," to indicate the degenerative features. Several other descriptive titles have been used. A review of the numerous reports may be helpful in drawing a general picture and in correlating the various opinions which have been advanced.

In 1926, Foix and Alajouanine[1] published a report of 2 cases which they believed represented a new disease entity, subacute necrotic myelitis. Clinically, their cases presented the following picture:

1. Progressive amyotrophic paraplegia, spastic at the start and later flaccid, advancing from below upward, with amyotrophy in the lower segments as the spasticity spread to the upper segments.
2. Sensory impairment, at first dissociated, later complete, with onset after some progress in the paralytic phenomena.
3. Albuminocytologic dissociation of the spinal fluid.
4. Subacute course, with fatal issue in one to two years.

The anatomic observations were quite distinctive in each case. Necrosis in the spinal cord chiefly affected the lumbosacral segments and tended to disappear in the midthoracic segments. The gray matter was involved predominantly, but the white substance was affected as well. The vascular changes were described as "endomesovascularitis," consisting of enormous hypertrophy of the large extramedullary vessels of the cord, the veins being affected more than the arteries. No obliteration of the lumens of the extramedullary or the intramedullary vessels was noted. The changes were distinct from those of syphilitic arteritis, according to the statement of the authors. No etiologic factor was determined in either of the 2 cases described, and it was the opinion expressed by these investigators that some toxic or infectious agent had affected simultaneously the media of the vessels and the parenchyma of the cord.

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Read (in part) before the Section on Neurology and Psychiatry of the Medical Society of the District of Columbia, Feb. 5, 1942.

1. Foix, C., and Alajouanine, T.: La myélite nécrotique subaiguë, Rev. neurol. **2**:1 (July) 1926.

TABLE 1.—*Cases Reported Under Heading of Necrotic Myelitis* *

Author and Date	Age, Yr.; Sex	History and Onset of Illness	Clinical Observations	Course and Duration	Spinal Fluid	Postmortem Observations
Foix and Alajouanine, 1926	29; male	Albuminuria at 16 years of age, bout of lumbar pain. Onset with progressive intermittent claudication	Atrophy of leg and thigh muscles. Reflexes active; ankle clonus +; Babinski sign —; sensation intact	Progressive weakness of lower extremities with flaccidity, areflexia and atrophy; dissociated sensory loss to L 5, progressing to complete anesthesia, to Th 12. Intestinal obstruction; pyuria; decubitus; death after 2 yr. and 9 mo.	Xanthochromia; massive hyperalbuminosis; slight lymphocytosis. Wassermann reaction —	Necrosis, maximal in lumbosacral segments; gray matter more predominantly involved than white. "Endomesovascularitis" of extramedullary vessels. Destruction of nerve cells, with demyelinated foci. Meningeal reaction, cells loaded with pigment
	27; male	Albuminuria; lead colic; no symptoms referable to nervous system prior to onset; sudden weakness of legs, progressive for 3 mo.	Paraplegia; knee jerks active; ankle jerks absent; sensory function intact; optic neuritis	Remission 3 mo.; then flaccid paraplegia, areflexia, atrophy and dissociated anesthesia to umbilicus; later complete. Death 11 mo. after onset	Xanthochromia; massive hyperalbuminosis; slight lymphocytosis. Wassermann reaction —	Parenchymatous and vascular changes similar to those in case 1. Numerous compound granular corpuscles; meningeal lymphocytic infiltration
van Gehuchten, 1927	34; female	Flaccid paraplegia with sensory impairment, ascending to upper extremities, 4 yr. previously, during pregnancy; disturbance cleared completely after 3 to 4 mo. Onset of present illness with delayed menses, headache, nausea; flaccid paraplegia and urinary retention after 48 hr.	Flaccid paralysis of lower extremities; areflexia; sensory loss for all modalities to Th 11	No alteration in neurologic picture. Cystitis; decubitus; downhill course, with intermittent fever; death 3 mo. after onset	Albumin 1,000 mg. per 100 cc.; numerous lymphocytes; (Wassermann reaction of blood —)	Cord much reduced in size from Th 6 down; degeneration of white columns; marked glial reaction; perivascular lymphocytic infiltration; necrosis from Th 10-S 2, with intense destruction, neuroglial proliferation, lymphocytic infiltrations and compound granular corpuscles. Hyperplasia of intramedullary and extramedullary vessels; small abscess in posterior column at S 1
Van Bogaert, Ley and Brandes, 1930	20; female	Pain in lower part of back, papular eruption, pains and paresthesia in lower limbs; fever, flaccid paralysis and urinary retention 10 wk. after first symptoms. Insomnia, myoclonic twitchings of abdominal muscles	Flaccid paralysis of lower extremities, with loss of reflexes; muscular atrophy; sensory level to Th 12; root pains from L 1 to S 1; incontinence	Sensory and reflex improvement. After several months, cerebral symptoms: trigeminal pain, headache, insomnia, ataxia, nystagmus, progressive blindness. Cerebral hypertension; decompression. death about 1 yr. after first symptoms	No examination	Necrosis in dorsal portion of cord, especially gray matter. Vascular hyperplasia with dilatation. Changes throughout central nervous system: lymphocytic infiltrations; foci of necrosis; glial proliferation; vascular hypertrophy
Lhermitte, Fribourg-Blanc and Kyriaco, 1931	50; male	Infectious episode with fever, followed by difficulty in locomotion and uncertainty of gait; no muscular weakness	Hyperreflexia; ankle clonus and Babinski sign bilaterally; absence of abdominal reflexes; sensory diminution to touch and pain almost to umbilicus	Increasing stiffness; spasticity; vesical impairment. Recession of sensory level; dissociation. Slowly progressive course; no muscular wasting. Craniotomy; paralysis; death. Duration 2½ yr.	40 lymphocytes; albumin 1.18 Gm. per 100 cc.; Wassermann reaction —	In dorsal portion of cord, homogenization of tissue, proceeding to cavity formation, rarefaction, gliosis and vascular proliferation
Marinesco and Draganesco, 1932	47; female	Pain in thighs, followed in 2 wk. by pain in neck, shoulders and lower limbs; inability to move legs	Flaccid quadriplegia with hyporeflexia; bilateral Babinski sign; dissociated anesthesia, with indistinct cervical level	Urinary retention; febrile course. Death in 5 wk.	1 cell; Pandy reaction —	Softening and hyperemia of cervical part of cord; necrosis of gray matter; spongy changes in white. Vascular hypertrophy; massive adventitial thickening. No inflammatory infiltration
	52;	Lightning onset, in 24 hr.	Complete flaccid paraplegia	Rapidly progressive, febrile course;	3 cells; Pandy reac-	Softening, Th 5-9; marked necrosis,

	52; male	Lightning onset, in 24 hr.	Complete flaccid paraplegia with hyporeflexia; dissociated anesthesia to Th 7; urinary retention	Rapidly progressive, febrile course; terminal loss of all sensation in lower extremities. Death 20 days after onset	3 cells; Pandy reaction 1+	Softening, Th 5-9; marked necrosis, Th 6. Vascular involvement, limited to surface vessels at level of destructive lesion. Hyperplasia; lymphocytic infiltration
Minéa, 1932	...	Sudden onset of blindness 5 yr. previously	Complete flaccid paraplegia; tendon jerks preserved but diminished		Yellow fluid, 46 cells; Nonne-Apelt reaction +	Necrosis less frank than in previous cases; vascular hypertrophy pronounced
Riser, Geraud and Planques, 1937	29; male	Generalized erythema following inoculation with antitetanus serum; weakness of lower extremities about this time; slowly progressive course	A year after onset, paraplegia, hyperreflexia, bilateral Babinski sign; loss of vibratory sense in lower extremities; difficulty in urination	Progressive sensory and motor impairment, reaching upper extremities in 2 yr.; slow development of flaccidity. Operative exploration; death 2 yr. and 7 mo. after onset	30 lymphocytes; albumin 2 Gm. per 100 cc.; Wassermann reaction doubtful	Encephalomyelitis: In brain, lymphocytic infiltrations, rarefied foci, gliosis, prominent perivascular hemorrhages. In cord, loss of form at C 7, spongy debris, marked hyperplasia of central vessels, cavity in sacral region
Zhitomirskaya and Ovcharenko, 1937	40; female	Typhus fever during year of onset; beginning of illness with general debility and weakness of legs	Spastic paraplegia; loss of pain sense below Th 10; suppression of urine	Within 4 mo. flaccid paraplegia and atrophy; anesthesia complete to Th 4. Temporary improvement, followed by recurrence, with paralysis and contractures of upper extremities and death within 1 yr. of onset	Normal	Cerebral cortex: degeneration of nerve cells, lymphocytic infiltrations, minute fresh hemorrhages, pale stain subcortex. Spinal cord; foci of necrosis from cervical to lumbar segments, diffuse degeneration of thoracic portion of cord, hyperplasia of small vessels, lymphocytic infiltrations, destruction of ganglion cells, necrosis most prominent in gray matter
	46; male	No past illness known. Onset with pain in right leg; paralysis next day	Flaccid paraplegia; areflexia; complete sensory loss to Th 10; urinary retention	Muscular atrophy in lower extremities; febrile course; death in 10 wk.	White corpuscles 3-5 per field; protein 2.69 Gm. per 100 cc.; Wassermann reaction —	(Acute endocarditis.) Cerebral cortex; degeneration, infiltrations, Spinal cord: necrosis at thoracic level, vascular hyperplasia, glial reaction, nerve cell degeneration, lymphocytic infiltrations, petechial hemorrhages
	35; female	Onset sudden, with chill, fever, impaired vision and loss of power in lower limbs	Flaccid paraplegia and areflexia of lower extremities; weakness of upper extremities; anesthesia to Th 5; urinary retention	Headache, nuchal rigidity, nystagmus, optic nerve atrophy; paralysis of hands, anesthesia to Th 3. Slight temporary improvement; death 2½ mo. after onset	Xanthochromia; protein 250 mg. per 100 cc.; 20 white cells per cu. mm.; Pandy reaction strongly +; Wassermann reaction —	Necrosis entire length of cord, maximal in thoracic region; white matter predominantly affected; increase in perivascular spaces; connective tissue formation; lymphocytic infiltrations and altered cells in cerebrum and petechiae in tuber cinereum
Juba, 1938	47; male	Pains, followed by weakness in lower extremities	Hypotonia; weakness; absence of reflexes in lower extremities; absence of abdominal and cremasteric reflexes; sensory level to Th 12; urinary retention	Course rapidly downhill; decubitus; febrile course; death after 8 wk.	Turbid; 680 cells per cu. mm.; Pandy reaction +++; protein 50 mg. per 100 cc.; Wassermann reaction —	(Carcinoma of stomach; metastases to omentum.) Cord amorphous and necrotic from midthoracic level down; destruction of gray and white matter; meninges heavily infiltrated, chiefly with leukocytes. Vascular hypertrophy, without obliteration of lumen; intimal splitting. Necrosis most marked near thickened vessels

TABLE 1.—*Cases Reported Under Heading of Necrotic Myelitis—Continued*

Author and Date	Age, Yr.; Sex	History and Onset of Illness	Clinical Observations	Course and Duration	Spinal Fluid	Portmortem Observations
Greenfield and Turner, 1939	37; female	Attacks of sciatic pain 5 yr. previously, which cleared after tonsillectomy; intermittent painless swelling of knuckles. Onset with numbness and weakness of right leg, then of left leg; incontinence	Flaccid paralysis, with areflexia of lower extremities; complete sensory loss to Th 10	Sensory level to Th 8; motor weakness of upper abdominal and intercostal muscles. Death with urinary infection 5 wk. after onset	18 cells, chiefly polymorphonuclears; 500 mg. protein per 100 cc.; Wassermann reaction —	Cord softened from Th 8-11 and L 4-S; lacunas, collagenous fibers from walls of vessels, frank necrosis; white columns chiefly affected. Small vessels and anterior spinal vein at L 3 thickened. Necrosis most marked near thickened vessels
	55; male	Gout; auricular fibrillation. Onset with numbness of left leg 7 mo. before admission; 1 mo. later, numbness of right leg and weakness of both lower extremities; urinary difficulty 4 mo. before admission	Weakness, atrophy, hypertonus and hyperreflexia of lower extremities; hypalgesia to Th 9 and total impairment of sensation below knees	Ascent of sensory level to Th 7. Laminectomy; death on 5th postoperatve day, 9 mo. after onset	1 cell; protein 100 mg. per 100 cc.; Wassermann reaction —	At Th 11-12, lacunar degeneration and necrosis, particularly of lateral and posterior columns; from Th 8 down thickening of anterior spinal vein; hypertrophy of intramedullary vessels
	61; male	Onset with pain in right leg, pain 3 mo. later in left; weakness after 6 mo.; urinary difficulty in 6½ mo.	Weakness of lower extremities, increased tone, no atrophy. Vibratory and position senses diminished in lower extremities; cutaneous sensation intact	Flaccidity in legs after 3 wk., flexor spasms, muscular atrophy; sensory impairment for all modalities to Th 10 after 2 mo. Death in 12 mo.	(1) 3 cells; protein 70 mg. per 100 cc.; Wassermann reaction —. (2) no cells; protein 100 mg. per 100 cc.	Lacunar degeneration and fenestration at Th 8-11; early necrosis of white and gray matter at Th 12; dense gliosis at Th 6, with surface vessels thickened and almost occluded; thickening of intramedullary vessels at Th 12-L 2
Draganescu and Lupascu 1940	43; male	Indisposition (cold) 3 days previously; pain in back and limbs, followed in a few hours by numbness and paralysis of legs; febrile course	Flaccid paralysis of lower extremities; areflexia; weakness of arms; global anesthesia to C 5-7; urinary retention; constipation	Total paralysis, including upper limbs; anesthesia to upper cervical segments; respiratory difficulty; dysphagia. Death 5 days after development of paraplegia	Fluid clear; Pandy reaction 3+; cells 2.9; protein 0.44 mg. per 100 cc.; Wassermann reaction —; culture sterile	Destructive process most intense from C 3-6; hemorrhagic softening; necrosis without histologic evidence of inflammation
Dansmann, 1940	28; male	Grip and mandibular abscess 5 wk. before admission. Onset with pain in legs; rapid impairment of locomotion	Weakness of lower extremities with hyporeflexia; sensory loss for all modalities to L 2	Ascent of sensory level to Th 7 after 1 day; paresthesias of hands; incontinence; decubitus. Death 6 wk. after onset, with ascending urinary infection	(1) 16 cells; protein 4.9 mg. per 100 cc. (normal 0.8-1.3 mg.). (2) 963 cells; protein 16.8 mg. (3) 28 cells; protein 2 mg.; Wassermann reaction —; culture sterile	Chronic, circumscribed caudal meningitis. Lowest segments completely destroyed; meninges thickened, with leukocytic infiltrations. Thoracic segments necrotic, particularly white matter, with circumscribed cellular infiltrations. Cervical segments necrotic, with syringomyelic cavity surrounded by gliosis. Adventitial collaring with lymphocytes

* In this table, and in the accompanying tables, levels in the cord are designated by letters and numerals: i. e., C, Th, L and S indicate cervical, thoracic, lumbar and sacral levels.

After this report, other cases were described under the same title. Some of these were similar to the cases of Foix and Alajouanine; others differed in many respects.

Van Gehuchten [2] described a case in which the onset was more rapid and the clinical course more acute. Here, the paraplegia developed within forty-eight hours; it was flaccid from the beginning, and no ascent was noted. The sensory loss was complete from the start. The protein content of the spinal fluid was 1,000 mg. per hundred cubic centimeters, and many lymphocytes were noted. The course of the disease was progressive, and death occurred three months after onset. Anatomically, necrosis was pronounced in the lower thoracic segments, involving the white and the gray matter. Vascular hyperplasia and dilatation were present, but not in a degree comparable to that seen in the original cases. Lymphocytic infiltrations were noted in some places, and in the first sacral segment a small abscess appeared. Van Gehuchten expressed the opinion that the necrotizing character of the disease did not speak for a specific etiologic factor and that a single infectious agent might produce various types of myelitis—infiltrative or degenerative, acute or subacute, with or without necrosis—depending on the degree of virulence. He postulated that many of the special forms of myelitis that have been described may all be referable to the same etiologic factor.

The next report to appear under the original designation was that of van Bogaert, Ley and Brandes.[3] These authors recorded a case with paraplegia which cleared after an acute onset, followed six months later by cerebral complications. Death followed operation for decompression. Anatomically, degenerative changes were noted, particularly in the thoracic portion of the cord, and were accompanied by vascular hyperplasia with dilatation. Throughout the central nervous system, however, there were abnormal foci, with lymphocytic infiltration, vascular hypertrophy, glia proliferation, cellular degeneration and necrosis.

Lhermitte, Fribourg-Blanc and Kyriaco [4] described a case in which the illness was of two and a half years' duration, with slowly progressive spastic paraplegia, which remained spastic until death, and without muscular wasting. Sensory loss was first dissociated and later complete, but without ascent of the level. Examination of the spinal fluid showed marked increase in protein and 40 lymphocytes per cubic millimeter. Postmortem examination revealed changes in the thoracic portion of the spinal cord, consisting of gliosis, vascular proliferation, rarefaction, homogenization of the parenchyma and cavity formation.

The following year Marinesco and Draganesco [5] reported 2 cases in which a more acute picture was presented. The clinical features included lightning onset of an acute febrile illness with flaccid paralysis and hyporeflexia, dissociated sensory loss (later complete in 1 case) and urinary retention. The cell and protein contents of the spinal fluid were normal in the first case, while in the second case there were 3 cells per cubic millimeter of fluid and a positive Pandy reaction. Death occurred after five and three weeks respectively. Necrosis was seen between the fifth to the eighth cervical segment in the first case and at the sixth thoracic segment in the second. The white and gray matter were involved in both instances,

2. van Gehuchten, P.: Un cas de myélite nécrotique aiguë, Rev. neurol. **1**:505 (April) 1927.

3. van Bogaert, L.; Ley, R. A., and Brandes, F.: Contribution anatomo-clinique à l'étude de la myélite nécrotique subaiguë de Foix-Alajouanine, Rev. neurol. **2**:1 (July) 1930.

4. Lhermitte, J.; Fribourg-Blanc, and Kyriaco, N.: La gliose angéio-hypertrophique de la moelle épinière (Myélite nécrotique de Foix-Alajouanine), Rev. neurol. **2**:37 (July) 1931.

5. Marinesco, G., and Draganesco, S.: Myélite nécrotique aiguë, Ann. de méd. **31**:5 (Jan.) 1932.

and vascular hyperplasia was particularly striking at the level of the lesions. In the first case no inflammatory changes were noted; in the second there were prominent lymphocytic infiltrations, especially about the veins, in the necrotic areas. These authors expressed the belief that the rapidity of the process in their cases, as well as in that of van Gehuchten, accounted for the less pronounced degree of vascular hyperplasia as compared with the hypertrophic changes described by Foix and Alajouanine. They pointed out, too, that the necrotic character of the parenchyma was not a specific feature, having been described in certain cases of herpes zoster, experimental encephalomyelitis, neuromyelitis optica and acute multiple sclerosis.

Minéa [6] reported a case with paraplegia, in which sudden onset of blindness had occurred five years previously. Anatomically, the spinal cord was the seat of degeneration, with somewhat less frank evidence of necrosis than that observed in the cases described previously. Vascular hypertrophy was outstanding.

Riser, Geraud and Planques [7] described a case of "subacute necrotic encephalomyelitis." Motor and sensory impairment extended to the upper extremities from a previous level at the sixth thoracic segment. The pathologic changes were those of necrotizing encephalomyelitis. In the cerebrum there were lymphocytic infiltrations, foci of rarefaction, gliosis, vascular occlusion and some perivascular hemorrhages. The spinal cord was noticeably softened and spongy at the seventh cervical segment.

Zhitomirskaya and Ovcharenko [8] recorded 3 cases, in the first of which the condition resembled the syndrome described by Foix and Alajouanine. Onset followed an attack of typhus fever. In the second and third cases the disease was of shorter duration, with a clinical course similar to that noted in van Gehuchten's case. In the second case acute bacterial endocarditis was present, and the possibility of embolic phenomena in the spinal cord must be considered. In the third case there were visual complications, and the condition was suggestive of neuromyelitis optica with involvement of the cord progressing to necrosis. These authors suggested that the clinical picture of flaccid paralysis and total anesthesia occurred as the result of involvement of the white matter of the cord in cases of so-called acute necrotic myelitis, whereas spastic paralysis and dissociated anesthesia could be correlated with lesions in the gray matter in cases of subacute necrotic myelitis.

Juba [9] described a case presenting the acute picture, with flaccid paralysis of the lower extremities and complete sensory loss to the twelfth thoracic segment. Postmortem examination revealed carcinoma of the greater curvature of the stomach and necrosis of the spinal cord, most pronounced in the midthoracic region.

Greenfield and Turner [10] reported 3 cases representing both the acute and the subacute type. They described three stages in the tissue alterations leading to necrosis, namely lacunar degeneration, mesodermal reaction and, finally, frank necrosis. These authors expressed the belief that the parenchymal lesions were wholly dependent on disease of the vessels and that the involvement of the intra-

6. Minéa, I.: Cas de myélite subaiguë d'origine infectieuse cryptogénétique, Bull. Soc. roumaine de neurol., psychiat., psychol. et endocrinol. **13**:27, 1932.

7. Riser; Geraud, and Planques: De l'encéphalomyélite nécrotique subaiguë, Rev. neurol. **67**:455 (April) 1937.

8. Zhitomirskaya, B. M., and Ovcharenko, E. P.: Concerning Necrotic Myelitis, Sovet. psikhonevrol. **13**:59, 1937.

9. Juba, A.: Myelitis necroticans subacuta (Foix-Alajouanine), Deutsche Ztschr. f. Nervenh. **148**:17 (Nov.) 1938.

10. Greenfield, J. G., and Turner, J. W. A.: Acute and Subacute Necrotic Myelitis, Brain **62**:227 (Sept.) 1939.

medullary vessels noted in cases of the acute type preceded that of the large surface vessels, the degeneration of which was prominent in cases of the subacute and chronic forms.

Draganescu and Lupascu [11] described the syndrome of Landry's ascending paralysis occurring in the course of acute necrotic myelitis.

In the same year (1940) Dansmann [12] recorded a case in which grip and mandibular abscess preceded the onset of symptoms of involvement of the spinal cord. The course was rapidly progressive, with death in six weeks. There was circumscribed chronic meningitis in the caudal segments, with complete destruction of the parenchyma of the cord. Necrotic foci were described as high as the cervical segments. The author concluded that the process had resulted from vascular dissemination of a bacterial infection and stated it was likely that a toxin rather than the organisms themselves caused the spinal lesions.

In this country, the term "necrotic myelitis" has been avoided. Moersch and Kernohan [13] recorded 3 cases under the title "progressive necrosis of the spinal cord," and Schunk and Kernohan [14] later added a case of similar nature with cerebral involvement.

In a discussion on the paper by Moersch and Kernohan,[13] before the American Neurological Association, Hassin stated that the condition under consideration is usually classified with the myelomalacias and that the cause is usually vascular (thrombosis or embolism), but that an infectious agent might produce a similar effect. Moersch and Kernohan maintained that the process was probably due to the action of some virus or toxin and should have a designation distinct from the myelomalacias, which are due to "purely vascular or so-called degenerative changes."

Moersch and Kernohan indicated the similarity between their cases and those of Foix and Alajouanine but pointed out that vascular changes were prominent in the French cases, while in their own, vascular hyperplasia appeared only in the first, and then involved the walls of the smaller vessels.

The reports of 6 earlier cases were reviewed by Moersch and Kernohan as representative of "progressive necrosis of the spinal cord." Most of these had been described under the heading of myelomalacia by Bassoe and Hassin,[15] Schmitt,[16] d'Antona,[17] Low [18] and Stone.[19] Feindel [20] had recorded his case as one of acute ascending necrosis of the spinal cord. The cases of Nonne,[21] Davison and

11. Draganescu, S., and Lupascu, G.: Sindrom de paralizie ascendenta de tip landry in cursul unei mielite necrotice acute, Rev. ştiinţ. med. **29**:210 (March) 1940.

12. Dansmann, W.: Ueber die sogenannte Myelitis necroticans subacuta, Ztschr. f. d. ges. Neurol. u. Psychiat. **168**:644, 1940.

13. Moersch, F. P., and Kernohan, J. W.: Progressive Necrosis of the Spinal Cord, Arch. Neurol. & Psychiat. **31**:504 (March) 1934.

14. Schunk, P., and Kernohan, J. W.: Progressive Necrosis of the Spinal Cord, with Cerebral Involvement, Rocky Mountain M. J. **36**:789 (Nov.) 1939.

15. Bassoe, P., and Hassin, G. B.: Myelitis and Myelomalacia, Arch. Neurol. & Psychiat. **6**:32 (July) 1921.

16. Schmitt, W.: Ueber akute Rückenmarkserweichung (Myelomalacie), Deutsche Ztschr. f. Nervenh. **72**:78 (Jan.) 1921.

17. d'Antona, S.: Sulla necrosi spinale acuta nel corso dei tumori maligni, con un contributo alla conoscenza delle "ernie spinali malaciche," Neurologica **3**:65 (April) 1926.

18. Low, A. A.: Acute Ascending Myelomalacia, with Clinical Picture of Landry's Paralysis: Clinicopathologic Report of Case, Arch. Neurol. & Psychiat. **21**:594 (March) 1929.

19. Stone, T. T.: Myelomalacia, Arch. Neurol. & Psychiat. **21**:718 (March) 1929.

20. Feindel, R.: Ueber akute aufsteigende Rückenmarksnekrose, Ztschr. f. d. ges. Neurol. u. Psychiat. **68**:147 (July) 1921.

21. Nonne, M.: Myelodegeneratio transversa carcino-toxaemica, Med. Klin. **2**:943, 1919.

TABLE 2.—*Cases Classified by Moersch and Kernohan Under Heading of Progressive Necrosis of the Spinal Cord*

Author and Date	Age, Yr.; Sex	History and Onset of Illness	Clinical Observations	Course and Duration	Spinal Fluid	Postmortem Observations
Nonne, 1919	65; male	Old chronic cough; clinical duodenal ulcer. Two weeks' history of weakness of legs and urinary retention	Weakness of lower extremities, diminished reflexes; sensory diminution for all modalities to umbilicus; sphincter paralysis	Total paralysis and complete anesthesia to umbilicus, after temporary remission; death 2 mo. after onset of spinal symptoms	Xanthochromia; globulin +++; no lymphocytes	(Carcinoma: lungs, hilar nodes, thyroid, retroperitoneal glands and vertebral bodies Th 8-12; no destruction of vertebrae; interspaces normal; no metastases to meninges or cord.) Cord softened in thoracic region; degeneration of nerve fibers and myelin sheaths, with failure to take stain; many phagocytic cells; vessels increased in number and thickened
Bassoe and Hassin, 1921	45; female	Sore throat 7 wk. previously. Onset with weakness of lower extremities; febrile course	Motor and sensory impairment of lower extremities; hyperreflexia; pallor of right optic disk	Progress of motor and sensory impairment to level of 4th rib; flaccidity of extremities in 2 days; disappearance of tendon jerks in lower extremities; death after 5 mo.	26 cells; globulin +; Wassermann reaction weakly +, later —; gold curve 4333211100	Thoracic portion of cord semifluid; cavity formation; demyelination; gitter cell infiltration; glial reaction; no inflammation
Feindel, 1921	23; male	Amputation of left leg at midthigh few months previously; radiotherapy. Two injections of arsphenamine with no reaction at time	Fever; flaccid paralysis of lower extremities; ascent of motor and sensory level to arms	Respiratory paralysis; death 3 wk. after onset	No examination	Lumbar and thoracic portions of cord swollen and reddish; demyelination; gitter cell infiltration; no inflammatory reaction; vessels not remarkable
Schmitt, 1921	17; male	Infection of tongue 1 mo. previously. Onset with weakness of left leg	Weakness, more in left lower extremities; spasticity, ataxia, hyperreflexia on left side, with Babinski sign	Motor and sensory loss to waist; deep reflexes of lower extremities absent; flaccidity on 3d day. Pains in arms and chest; death in 8 wk.	(1) 14 cells; globulin 1+; Wassermann reaction —. (2) Yellow fluid; cells 1,052	Marked softening; degeneration maximal from Th 4 to L 1; other regions of degeneration from C 5 to filum; no inflammatory changes
d'Antona, 1926	41; male	Adenocarcinoma of lung (metastases to ribs and liver). Sudden onset of paralysis of lower extremities; urinary retention	Motor and sensory paralysis to umbilicus, with diminution of deep reflexes	Ascent of motor and sensory loss to nipple line. Rapidly downhill; death after 8 wk.	Yellow fluid; many erythrocytes, polymorphonuclears, a few lymphocytes; globulin 1+; protein 60 mg. per 100 cc.; Wassermann reaction —	Cord gelatinous, herniated; many small nodules from Th 5 to L 3; pronounced necrosis; no inflammation
Low, 1929	30; female	Induced abortion few weeks prior to onset. Severe pain in lower extremities; numbness; paralysis	Flaccid paraplegia, with loss of reflexes in lower extremities; complete sensory loss to Th 10; fever	Ascent of sensory loss to clavicles in 1 mo.; death with respiratory difficulty in 9th wk.	338 cells; globulin 1+; Wassermann reaction —	Softening of lower thoracic, lumbar and sacral segments; no thrombosis; moderate lymphocytic infiltrations; marked perivascular infiltrations in cervical region; cord creamy and cavitated in softened areas

Stone, 1929	26; female	One wk. after attack of influenza, pain in legs; 3 wk. later, paralysis of left, then right, lower extremity, with ascent to upper extremities	Flaccid tetraplegia; loss of deep reflexes in lower extremities; sensory loss to clavicles, complete to umbilicus	Death in 6 wk., with ascending syndrome	Normal	Areas of softening from cervical to lumbar region; gitter cells numerous; no thrombosis or inflammation; glial proliferation; capillary increase
Davison and Keschner, 1933	28; male	Onset with sensation of cold in left leg and delayed thermal perception in both legs; urinary incontinence 9 wk. later	Complete paraplegia of upper neuron type; ataxic tremor and atrophy of muscles of hand, especially on right; loss of all forms of sensation below Th 2. Ptosis, nystagmus, anisocoria, corneal hypesthesia, deviation of uvula	Flexion contractures; atrophy of leg muscles; sensory level to C 4; diaphragmatic action impaired; febrile course; bed sores; death 10 mo. after onset	Pressure increased; 70 cells per cu. mm.; globulin 3+; Wassermann reaction —	Cord softened above lumbar and below cervical enlargement; thoracic portion only a shell; cavitations; numerous compound granular corpuscles about vessels; no lymphocytes
Moersch and Kernohan, 1934	37; male	Tightness; pain in legs; numbness below knees. Next day patient unable to move legs, incontinent	Complete sensory and motor loss to Th 12. Tendon reflexes absent; lower abdominal reflexes absent; upper abdominal reflexes present	Ascent of sensory loss to nipple line; febrile course, with decubitus and pyelitis; death in 5 wk.	(1) Numerous red blood cells. (2) Yellow fluid; 235 white cells; protein 60 mg. per 100 cc.; globulin 1+; Kolmer reaction —	Cord soft, completely necrotic in lumbar region; demyelination; some destruction of axis-cylinders; slight inflammatory reaction; moderate scavenger cell reaction; no glia. Cord herniated in some places
	28; female	Recurring tonsillitis. Onset with numbness in feet; coldness and weakness. In 5 days paralysis to waist	Flaccid paralysis and complete anesthesia to Th 7; loss of reflexes; pallor of left optic disk	Ascent of sensory loss to C 8; febrile course; death in 4th wk.	(1) 11 lymphocytes; globulin 1+; partial block; Kolmer reaction —	Cord soft from C 5 to Th 12; normal markings obliterated; marked necrosis of white matter, less of gray; degeneration of myelin and axis-cylinders. Scavenger cells numerous; inflammation absent; central canal dilated
	17; female	Burn on back failing to heal; squamous cell carcinoma; abscess of breast. Onset with pain in right arm and thorax; next day numbness from hip to knee, then inability to move legs	Paralysis and sensory loss to Th 4 on 4th day; impairment of bladder and bowel controls. Reflexes not noted	Increasing weakness; decubitus; pneumonia; death in 2 wk.	8 cells (6 lymphocytes); protein 160 mg. per 100 cc.; globulin +; colloid gold curve 4141333332; Kolmer reaction —; culture sterile	Profound necrosis of entire cord below thoracic segments (not examined above); no metastases; destruction of myelin and fragmentation of axis-cylinders; surface of cord nodular, with herniations; no reaction of any kind
Schunk and Kernohan, 1939	38; male	Onset with weakness and numbness of left leg, rapidly progressing to paralysis of all extremities in course of 4 days	Paralysis of all extremities; hyperreflexia; clonus; bilateral Babinski sign; sensation diminished generally	Respiratory paralysis, followed by temporary improvement in upper segments; febrile course; complete paralysis of lower limbs; complete anesthesia to Th 8; diminished reflexes; absence of Babinski sign. Death about 6 wk. after onset	10 cells, Pandy reaction 1+	Lumbar portion of cord swollen, dark, softened, hemorrhagic and semifluid; thoracic portion soft. No cellular reaction; cord completely necrotic; vessels dilated. In brain, many foci of softening, limited to white matter

Keschner [22] and Winkelman and Eckel [23] were mentioned as falling possibly under the same classification.

In Nonne's case softening of the spinal cord appeared to have developed as the result of toxic absorption from a nearby malignant tumor. The occurrence of spinal softening or necrosis in cases with malignant tumors elsewhere will be discussed later.

The case described by Winkelman and Eckel was one of myelomalacia secondary to impaired vascular supply, possibly the result of syphilitic endarteritis. It may be excluded from the group under consideration. Details of the other cases are given in table 2.

A search of the literature has revealed several additional scattered case reports, which are similar in many respects to those already noted. Collins [24] described 2 cases in which the origin was obscure and there was pronounced destruction of the cervical segments. Harbitz [25] recorded a case in which the disease apparently complicated influenza. Borromeo's [26] case was reported as one of degenerative transverse myelitis, and Behr and Wuite [27] diagnosed the condition in their cases as "ascending transverse myelitis." The case described by Spigel [28] was unique in that the disease occurred in a 3 year old child. The cases of Melikov [29] and Aksel and Kirçak [30] may be included in this group. In the case recorded by Silbermann [31] there were a number of possible etiologic factors, namely, parental syphilis, trauma and an anginal infection. Frymire [32] and Stone and Roback [33] reported cases in which the onset followed lifting of heavy weights or back strain. Markiewicz [34] cited the case of Neel [35] in his discussion of colloidal degeneration in the nervous system. He described the process of "colloidal degeneration," noted in a number of diseases of the nervous system, as the counterpart of amyloid degeneration in other organs. He asserted that vascular changes precede parenchymatous degeneration of a similar nature and that there occurs a spread of some toxic substance from the blood vessels. The process was differentiated from that

22. Davison, C., and Keschner, M.: Myelitic and Myelopathic Lesions: Clinicopathologic Study, Arch. Neurol. & Psychiat. **29**:600 (March) 1933.

23. Winkelman, N. W., and Eckel, J. L.: Focal Lesions of the Spinal Cord Due to Vascular Disease, J. A. M. A. **99**:1919 (Dec. 3) 1932.

24. Collins, J.: Acute Myelitis and Thrombotic Softening of the Spinal Cord, Rev. Neurol. & Psychiat. **10**:159, 1912.

25. Harbitz, F.: Patologisk-anatomiske erfaringer ved influenza og dens komplikationer, Norsk mag. f. lægevidensk. **81**:46 (Jan.) 1920; cited by Bassoe, P.: Nervous and Mental Diseases, Practical Medicine Series, Chicago, Year Book Publishers, Inc., 1920, p. 20.

26. Borromeo, G.: Su di un caso di mielite trasversa degenerativa a decorso subcronico, Policlinico (sez. prat.) **38**:295 (March 2) 1931.

27. Behr, E., and Wuite, J.: Myelitis transversa ascendens, Acta psychiat. et neurol. **10**: 657, 1935.

28. Spiegel, H. A.: Myelomalacia in a Three Year Old Child, Arch. Pediat. **53**:500 (July) 1936.

29. Melikov, M. M.: Pathogenesis and Pathologic Anatomy of Ascending Myelomalacia, Sovet. psikhonevrol. **13**:52, 1937.

30. Aksel, I., and Kirçak, V.: Les myélites de nature inconnue, Arch. balkan. med. chir. **1**:27, 1939.

31. Silbermann, J.: Ueber einen besonders schweren Fall von infektiös-toxischer Myelitis mit weitgehender Zerstörung des Rückenmarks, Ztschr. f. d. ges. Neurol. u. Psychiat. **116**: 140, 1928.

32. Frymire, W. A.: Acute Spinal Cord Degeneration with a Case Report, Illinois M. J. **61**:439 (May) 1932.

33. Stone, L., and Roback, H. N.: Myelomalacia Without Thrombosis Following Indirect Trauma (Strain), J. A. M. A. **108**:1698 (May 15) 1937.

34. Markiewicz, T.: Zur Frage der "kolloiden" Degeneration und ähnlicher Vorgänge in Zentralnervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **159**:53, 1937.

35. Neel, A. W.: Die Bedeutung der Eiweissvermehrung ohne gleichzeitige entsprechende Zellvermehrung in der Spinalflüssigkeit, Deutsche Ztschr. f. Nervenh. **117-119**:309, 1931.

of coagulation necrosis, described by Markiewicz,[36] although foci of necrosis did occur, with spongy changes, deposition of "colloidal" particles and "foam cell–like structure" of the endothelium of the smaller vessels.

The cases of morbid softening of the spinal cord reported by Gleckler [37] were not accompanied by clinical descriptions and cannot be considered in this series.

Table 3 presents a summary of the details in the aforementioned cases.

Prior to discussion of several of the features included in this review, 4 additional cases, with postmortem studies, may be described.

REPORT OF CASES

CASE 1.—*History.*—L. J., a Negress aged 42, was admitted to the hospital on Sept. 26, 1940. She dated the onset of her illness to July 1940, at which time she had severe constipation for one week. The left leg became weak at that time, and for a month she got around with a cane. Weakness of the left arm appeared shortly after the onset, with a great deal of pain across the left shoulder and over the extensor surface of the arm and hand. The arm became flexed and clawlike. About a month after the onset the right leg began to weaken, but was without pain. She began to note twitching and tremors in the legs, which would "draw up" involuntarily. Sore throat and some difficulty in swallowing appeared. Three weeks before admission she was compelled to stay in bed because of weakness in the lower extremities. Constipation became persistent, and urgency of urination appeared.

The past history included sinusitis three years prior to admission and hypertension known to have been present for six years.

Examination.—On admission the temperature was 98 F., the pulse rate 78 and the respiratory rate 18. The blood pressure was 150 systolic and 95 diastolic. The cranial nerves were not remarkable except for vertical and horizontal nystagmus and conduction deafness of the right ear.

The lower extremities were spastic, with atrophy of all muscle groups, and only slight motion was present. The upper extremities were weak bilaterally, the left more than the right. The left forearm was held in flexion, with the hand flexed and spastic. There was significant atrophy of the intrinsic muscles of the hand, as well as those of the arm and forearm. There was marked resistance to passive motion, with considerable pain. The reflexes were hyperactive in the upper and lower extremities; the Hoffmann sign was positive and the Mayer reflex negative bilaterally; ankle and patellar clonus and the Babinski sign were elicited bilaterally. The abdominal reflexes were absent. Sensory changes consisted of an increased threshold for position sense in both hands and in the toes; otherwise no impairment was noted.

Lumbar puncture revealed clear, colorless fluid under normal pressure. The manometric readings were normal. There were 20 cells per cubic millimeter, with lymphocytes predominating, and the total protein measured 175 mg. per hundred cubic centimeters.

Course.—On October 6, about ten days after admission, reexamination revealed that the picture had changed to one of profound hypotonia below the waist. Voluntary power in the legs was completely gone, and the patient was totally incontinent. The upper extremities were unchanged. Sensory examination at this time revealed hypesthesia, hypalgesia and thermanesthesia below the eighth cervical segment, with loss of deep sensation from the sixth thoracic segment down. Saddle anesthesia was complete, and a sweating level was noted at the fifth thoracic segment.

Lumbar puncture now revealed albuminocytologic dissociation, with a positive Pandy reaction, a total protein content of 100 mg. per hundred cubic centimeters and 3 cells per cubic millimeter, 2 of which were lymphocytes and 1 a polymorphonuclear leukocyte. The Kahn reaction of the spinal fluid was negative, and the colloidal gold curve was 4332211100.

On October 16 mass reflexes appeared, and there was loss of tendon reflexes in the lower extremities. A spiking temperature was noted on October 20, as the result of an ascending infection of the urinary tract, and at this time examination revealed atrophy of

36. Markiewicz, T.: Zur Frage der "Koagulationsnekrose" im Zentralnervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **159**:27, 1937.

37. Gleckler, H. E.: Two Cases of Morbid Softening of the Spinal Cord, Odessa M. J. **2**:337, 1927.

TABLE 3.—*Additional Cases from Literature Similar to Those Listed in Tables 1 and 2*

Author and Date	Age, Yr.; Sex	History and Onset of Illness	Clinical Observations	Course and Duration	Spinal Fluid	Postmortem Observations
Collins, 1912	29; female	Four mo. previously, transient blindness and pain in face. Onset with paresthesias of extremities; pain and difficulty in walking a week later	After 2 wk. tetraplegia, flaccid in upper extremities; ankle clonus and bilateral Babinski sign; reflexes present in lower and absent in upper extremities; sensory loss in all extremities; hypesthesia to 5th rib; urinary retention	Signs of upward extension; laminectomy performed; death 5 wk. after onset of spinal symptoms	Lymphocytes increased; Wassermann reaction —	(Limited to cervical segments of cord.) C 3 to C 6: extensive softening; hemorrhages; vessels engorged; heavy cellular infiltrations; fatty granular corpuscles, erythrocytes and products; vessels not remarkably altered
	38; female	One week after childbirth, pain in small of back; urinary retention; obstipation; numbness and weakness of lower extremities	Weakness of all extremities; tendon reflexes present, later exaggerated in lower limbs, with Babinski sign and clonus; abdominal reflexes absent on right; complete anesthesia below clavicles	Anesthesia above clavicles; difficulty in deglutition and respiration; complete paralysis of extremities; absence of knee jerks. Death following laminectomy 2 mo. after onset	No increase in cells	(Limited to cervical cord.) Cord soft, pulpy, shapeless; white and gray matter destroyed. Blood vessels infiltrated. Numerous cellular accumulations; gitter cells; glial overgrowth; neural elements degenerated
Harbitz, 1920	52; female	Influenza, followed by headache and papillitis; blindness in 2 wk.; pain and sensory diminution in both legs	Weakness of trunk and extremities; anesthesia below axilla	Death 2 mo. after onset	.....	Spinal cord softened in upper third, grayish red, edematous. Marked degeneration, maximal at Th 1, no inflammation
Silbermann, 1928	21; male	Father tabetic; injury to back, with apparent recovery, followed in a week by gingivitis, angina and fever. A week later, sudden onset of weakness, spreading to both legs, with complete sensory loss to knees. Ascent of anesthesia	12 hr. after onset flaccid paralysis of lower extremities and weakness of neck and trunk; sensory loss to cervical region; paralysis of bladder and bowel	Recession of sensory and motor loss to Th 8 in 6 wk.; transient facial palsy; downhill course; muscular atrophies; decubitus; death 1¼ yr. after onset	Normal	No recognizable structure of cord below Th 9; necrosis, cavitation, demyelination; peripheral gliosis; marked accumulations of fatty granular corpuscles; small vessels hypertrophied
Borromeo, 1931	18; male	Onset with pain and paresthesias in lower limbs, followed by ataxia and difficulty in locomotion	Weakness of lower extremities; atrophy of calf muscles; ankle jerks absent; ataxia; Babinski sign absent; thermanesthesia over area S 2-S 3	4th month: complete flaccid paraplegia, areflexia, sensory loss S 1-S 2; partial in L 5; later complete sensory and motor loss to groin. Septic course; bed sores; death in 7th mo.	Slight xanthochromia; 20 cells (lymphocytes); Pandy reaction 4+; Wassermann reaction —	Cord gelatinous from lower dorsal portion down. Complete destruction of all elements. Vessels unaltered except for obliterative thromboangiitis of a single arteriole
Frymire, 1932	37; male	Onset of weakness and numbness of left leg shortly after lifting of heavy weight; pain in back	After 1 wk., flaccid paraplegia, areflexia, sensory loss to Th 9	Febrile course; toxemia; decubitus; death 2 wk. after first examination	Fluid cloudy; numerous cells; protein content not recorded	Softening of cord at Th 9 to Th 10; substance exuded on opening of dura. Dropping out of white columns. In other regions, nerve degeneration and formation of fat granules

Behr and Wulfe, 1935	12; male	Patient fell on pointed object 3 mo. prior to onset; pain disappeared after 1 day. Onset with ataxia, difficulty in walking, pain in back	Flaccid paralysis of lower limbs; areflexia; sensory loss in lower limbs, later reaching nipple line	Ascent of sensory loss to upper extremities, with flaccid paralysis and complete sensory loss; death with respiratory difficulty on 7th day	Yellow; numerous polymorphonuclears; Pandy reaction ++	Cord pulpy, shapeless. Lumbar meninges thick with leukocytes; perivascular infiltrations. Hemorrhagic exudate. Parenchymal cavitation; demyelination; degeneration of ganglion cells. Reactive glial changes. Structure of cervical and thoracic segments better preserved
	35; male	Pain in back, numbness; later weakness of legs. Sensory loss to umbilicus; urinary difficulty; febrile course	Complete paraplegia with loss of reflexes; sensory loss to xiphoid cartilage; urinary retention; nuchal rigidity	Ascent of sensory level to C 8; crisis; return of temperature to normal and recession of sensory level to Th 4 or 5. Muscular atrophy, stationary for few weeks. Urinary infection; decubitus; death in 7th mo.	(1) Slightly turbid; pressure elevated; 15,000 cells (polymorphonuclears; few red blood cells); Pandy reaction ++; (2) Decrease in pressure, turbidity, cells and protein	Complete softening of cord from Th 4 down; partial softening as high as C 5. Hemorrhagic foci; compound granular corpuscles; reactive gliosis; lymphocytic infiltrations; degeneration of myelin
Spigel, 1936	3; female (colored)	Onset at age of 2½ yr. with backache, then pain in right knee and difficulty in walking. Papular urticaria; swelling of extremities	Flaccid paralysis and atrophy of muscles of back and extremities; inability to support head. Areflexia; no response to pinprick anywhere. Passive motion painful	Paralysis of respiration and deglutition. Febrile course; terminal pneumonia; death 3 wk. after admission	Fluid clear, colorless. No cells; protein normal, smears and culture negative	Thoracic portion of cord most affected; areas of degeneration; cavitation of gray matter. Vacuolation of white matter at other levels; cavities filled with necrotic material; no leukocytes
Melikov, 1937	30; male	Recent attack of malaria; grip just preceding onset. Pain in lower limbs; 4 days later complete paralysis of legs	Complete paralysis of lower extremities; hypertonus. Hyperreflexia of upper and lower limbs; Babinski sign bilaterally; anesthesia to Th 9; urinary retention; slight weakness of left side of face	Ascent of sensory level to C 8; paralysis of upper extremities. Tonus in low extremities diminished. Reflexes first hyperactive, later diminished. Nuchal rigidity; respiratory paralysis; death in 3 wk.	(1) Fluid turbid; 13 cells; Pandy reaction ++; (2) Cloudy, leukocytes. Pandy reaction ++++	(Pleural effusion on right side; atelectasis.) Spinal meninges agglutinated by exudate. Lower thoracic and upper cervical segments disintegrated. Minute hemorrhages; little inflammatory reaction
Stone and Roback, 1937	31; female	Injury to right arm in fall 4 mo. previously; atrophy of small muscles of hand. "Head cold"; backache on day before onset. Patient pulled herself up on a tree; sudden numbness of right leg	Flaccid paralysis of lower and weakness of upper extremities ("cervical cord position"). Reflexes sluggish in lower and hyperactive in upper extremities; abdominal reflexes absent. Sensory level complete to C 8 to Th 1; urinary retention; febrile course	Recession of sensory level to Th 3; slight spasticity in lower extremities; improved motion but atrophy in upper extremities. Decubitis; toxicity; death after 10 mo.	(1) 2 cells; Pandy reaction —; protein 23 mg. per 100 Cc. (2) Erythrocytes. (3) Manometric block. (4) After 3 mo. fluid clear; no block; Pandy reaction —	(Spinal cord only.) softening from C 6 to Th 2; cord shrunken, shell-like; meninges thick. Gliosis, gitter cells and small perivascular infiltrations with lymphocytes. Vessels collapsed; intimal and adventitial proliferation
Aksel and Kirçak, 1939	21; male	Onset 1 mo. earlier, with lumbar pain, numbness over right half of body and later left half. Weakness; incontinence	Flaccid paraplegia, areflexia, anesthesia; upper extremities hypotonic. Anesthesia of trunk from costal margin to umbilicus, and hypesthesia posteriorly below Th 10. Absence of abdominal and cremasteric reflexes	Urinary infection; death 6 wk. after onset	Normal	Demyelinated foci, not delimited. Lesions in gray matter and about central canal. New vessels formed; cells about vessels filled with lipoid. Neuroglial proliferation; ganglion cells intact; inflammation minimal

the intrinsic muscles of the right hand and forearm. Decubitus ulcers appeared over the sacrum. The skin over the thorax and neck became tough, dry and scaly. Light stroking over the left arm caused exquisite pain. Terminally, there developed trismus and rigidity of all extremities, including the previously flaccid legs. Death occurred on December 17.

Necropsy.—The significant systemic observations were bronchopneumonia, cystitis and pyelonephritis.

On palpation the lower cervical region of the spinal cord appeared softened, with bluish discoloration of its surface. Section after fixation revealed marked destruction in this portion of the cord, with extensive softening and fissuring. The sectioned surfaces appeared yellowish translucent in some areas and whitish opaque in others. These changes extended downward through the upper thoracic segments.

Microscopic preparations revealed widespread destruction throughout the cervical portion of the cord, particularly on the left side. The gray and the white substance were equally involved, with complete disruption of the structure of the cord. The white columns appeared spongy, as the result of formation of lacunas where the myelin sheaths had been destroyed. Numerous areas of cavitation were noted. In many areas mesodermal elements appeared, in

Fig. 1 (case 1).—Destruction of white and gray matter in the cervical segment, particularly on the left side. Weigert stain; × 8.5.

the form of collagenous fibers, particularly about hyperplastic blood vessels. In the regions showing more complete destruction there were acellular and homogeneously stained areas, with infiltrations of lymphocytes, a few polymorphonuclear leukocytes and many macrophages. (The changes in this region corresponded to those described by Greenfield and Turner[10] as lacunar degeneration, mesodermal reaction and frank necrosis.)

On the left side the ganglion cells of the gray horns were almost completely destroyed. On the right side the ventral horn cells were fairly numerous, with moderately advanced degeneration in the form of chromatolysis and pyknosis.

The blood vessels were extremely hyperplastic. The intima and media were chiefly involved, particularly in the large extramedullary vessels in the cervical segments. Here the media presented a thickened lamellation, suggestive of the "onion skin" appearance described by Foix and Alajouanine, but to a lesser degree. Within the substance of the cord at these levels, all of the small vessels showed pronounced hypertrophy, with thickened intima and narrowed lumen. Vascular packets, with small branching, hypertrophic vessels, were seen in some regions. Numerous fat-containing granular corpuscles were noted.

At the other level degenerative changes were less advanced. Secondary degeneration was seen, particularly in the lateral columns. Vascular hyperplasia was limited more strikingly to the smaller vessels. Degenerative reaction was widespread among the ganglion cells. There were no significant changes in the brain or the brain stem.

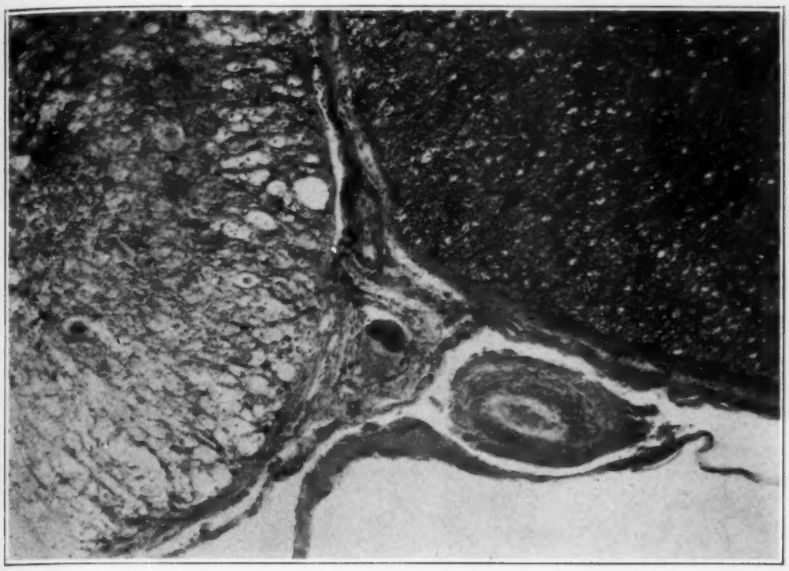

Fig. 2 (case 1.).—Hyperplasia of the large extramedullary vessels of the cervical region, suggestive of "onion peel appearance." Hematoxylin and eosin stain; × 7.5.

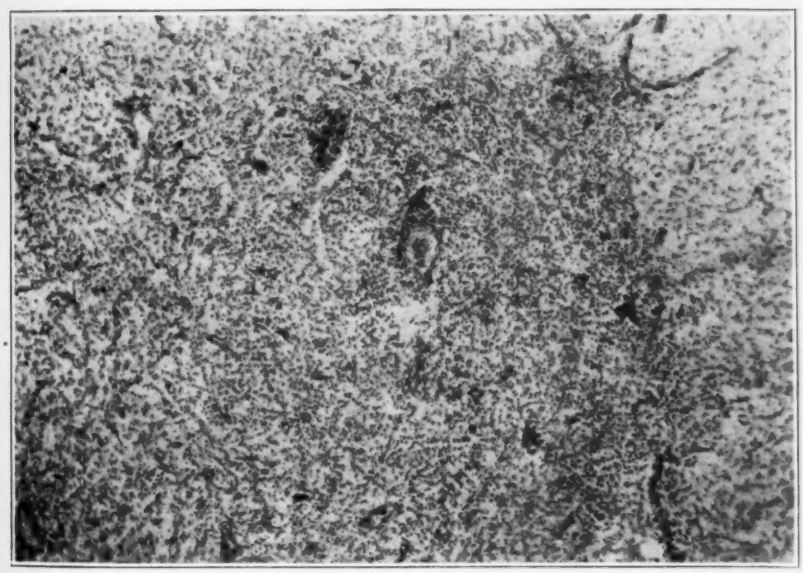

Fig. 3 (case 1).—Proliferation of small vessels of the cord, and pronounced inflammatory round cell infiltration into the white and gray matter. A few pyknotic ganglion cells may be seen. Thionine stain; × 7.5.

Case 2.—*History.*—M. F., a white woman aged 70, was admitted to the hospital on Sept. 17, 1940, complaining of pain in her chest and her right shoulder. She dated her complaints to July, two months previous to admission, when she strained her shoulder in lifting

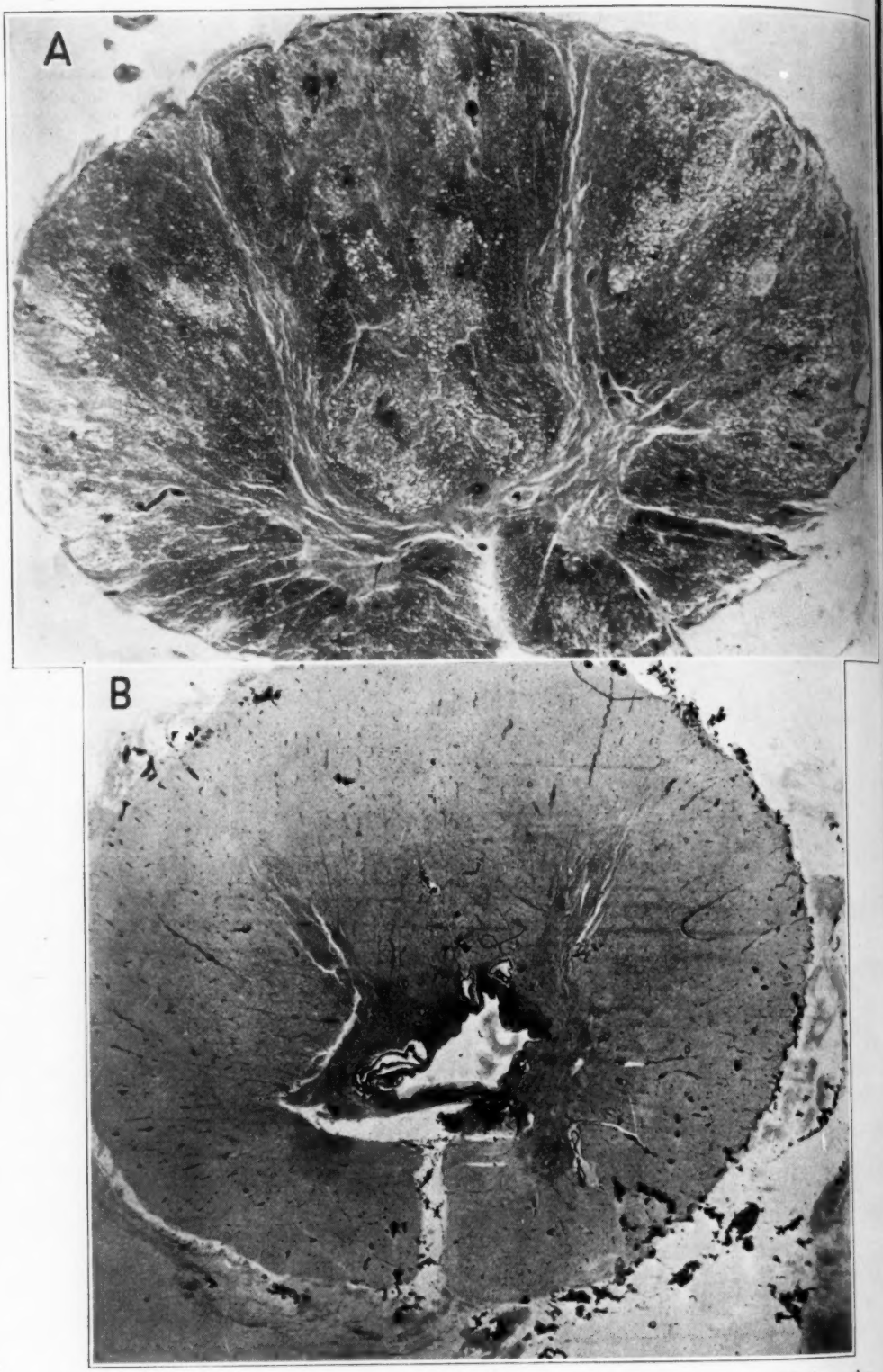

Fig. 4 (case 2).—*A*, patchy demyelination throughout the thoracic segments, with formation of lacunas. Weigert stain; × 10. *B*, fibrous gliosis surrounding cavity in midthoracic region. Holzer stain; × 10.

a weight. Since that time she had suffered pain in the right shoulder. In September, after another strain, she noted pain in her chest anteriorly and between the scapulas posteriorly. This pain was described as dull and constant and was aggravated during defecation and urination. Two days before admission she complained of weakness of both lower extremities, and this persisted. She could not empty her bladder except by pressing on her abdomen.

Examination.—On admission the temperature was 99 F., the pulse rate 80 and the respiratory rate 20; the blood pressure was 140 systolic and 80 diastolic. The pupils were pinpoint and reacted to light and in accommodation. The thyroid gland was uniformly enlarged and soft. The cranial nerves were normal. The lower extremities were weak bilaterally, but the reflexes were equal and active on the two sides. The abdominal reflexes were absent. The Babinski sign was not elicited. Position sense was diminished in the lower extremities, and vibratory sense was impaired as high as the iliac crests. There were hypesthesia and hypalgesia below the third rib anteriorly and the scapular spines posteriorly.

Course.—Weakness in the lower extremities was progressive, and reexamination on October 1 revealed the following changes: The pupils were small, the left being larger than the right, and both reacted sluggishly. There were nystagmus on lateral gaze and ptosis of the right lid. The lower extremities were completely paralyzed and flaccid. The knee and ankle jerks were absent; the abdominal reflexes were absent, and there was no response on

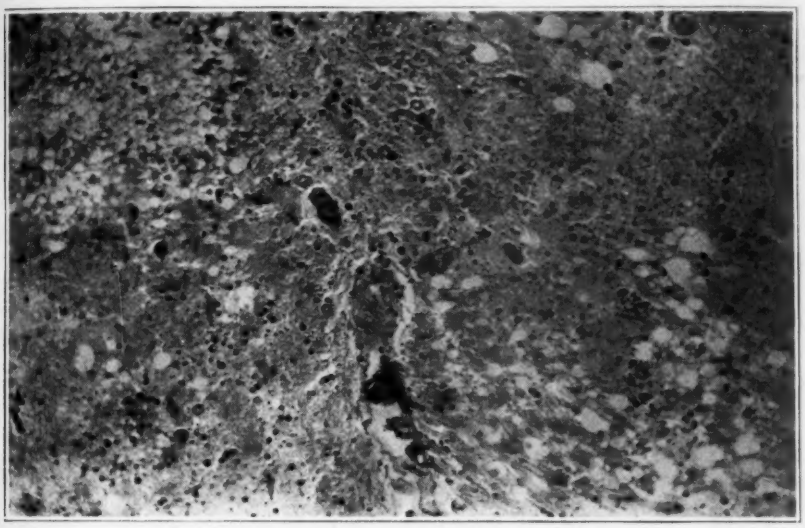

Fig. 5 (case 2).—Vacuolation or lacunar degeneration and frank necrosis; numerous corpora amylacea; hyperplasia of small vessels. Thionine stain; × 75.

plantar stimulation. Marked relaxation of the sphincters was noted. Weakness extended to the upper extremities bilaterally, the right arm being affected more than the left. The deep reflexes here were equal and active on the two sides, and the Hoffmann sign was not elicited. Sensory loss corresponded to that noted previously. Lumbar puncture on October 1 revealed a clear, colorless fluid, with a pressure of 75 mm. of water. There was no rise on jugular pressure, and the rise and fall on abdominal compression were normal. The Pandy reaction was 4 plus, with a total protein content of 750 mg. per hundred cubic centimeters. There were 2 cells per cubic millimeter, of which 1 was a lymphocyte and the other a polymorphonuclear leukocyte. The Kahn reaction was negative; the colloidal gold curve was 5554444320. The Kahn reaction of the blood was negative. The basal metabolic rate was +3 per cent. The electrocardiogram was suggestive of myocardial fibrosis. A roentgenogram showed generalized demineralization of all vertebrae, with early spondylitis.

The patient complained of almost continuous pain in the shoulders and chest and of numbness and tingling in both arms and legs. She became progressively weaker and more helpless, and there was considerable muscular wasting. On October 8 coma ensued, with Cheyne-Stokes respiration, irregular, feeble pulse and a fall in blood pressure, and the patient died.

Necropsy.—There were carcinoma of the thyroid gland, with questionable metastases to the kidney; senile emphysema, and toxic changes in the spleen and liver.

The brain appeared entirely normal on gross examination. On palpation the upper thoracic portion of the spinal cord was moderately softened. Section at the fifth cervical level revealed a dusky gray discoloration in both anterior horns.

In the lower cervical and the upper thoracic segments, numerous areas of reddish discoloration were seen throughout the substance of the cord, particularly within the lateral and posterior gray horns and in the adjacent white matter. In the midthoracic region, the central canal appeared enlarged. From the sixth to the tenth thoracic segments, a large cavity was centrally located, being of maximal size at the eighth thoracic segment, where it measured 2 mm. in diameter. Below this region, and extending down to the first lumbar segment, the gray matter about the central canal appeared softened and mottled. The most caudal segments appeared normal on gross examination.

Microscopic preparations revealed extensive patchy demyelination throughout the upper thoracic region, imparting a diffuse moth-eaten appearance. Widespread fragmentation and formation of lacunas were noted where the myelin sheaths had been destroyed. The axis-cylinders were considerably swollen, and numerous compound granular corpuscles were seen. The neurons were pyknotic and shrunken and stained homogeneously. Chromatolysis and nuclear destruction were prominent. In the midthoracic region, the central portion of the cord was occupied by a large cavity. This extended from the region of the central canal into the adjacent gray matter. Pronounced gliosis, chiefly of the fibrous type, was seen surrounding this cavity.

The blood vessels, particularly in the areas which showed the most profound degeneration, were the seat of advanced changes. Hypertrophy of the intimal and the subintimal layer accompanied extreme narrowing of the lumen in the small vessels within the cord. Thrombosis and hemorrhage occurred in several of these vessels. The larger surface vessels, as well as the penetrating branches, showed moderate hyperplastic changes. No significant inflammatory infiltrations were seen.

The cerebral hemispheres and the brain stem presented no significant alterations.

CASE 3.—*History.*—J. M., a white man aged 36, was admitted to the hospital on April 20, 1942, complaining of weakness of the left leg and numbness and tingling of the right leg. About ten days previously he had noted cramplike pains in the right thigh. Two days later his left foot dragged and the leg felt heavy. Weakness was progressive, and a deep, dull pain persisted. Numbness of the right leg appeared a few days after the onset, and the extremity became tired easily and was somewhat weakened. The history was otherwise unrevealing.

Examination.—There was decided weakness of the left lower extremity, involving the thigh, leg and foot. The patient could lift the heel to the knee, but could not dorsiflex or plantar flex the foot, nor could he wiggle the toes. The deep reflexes were hyperactive in this extremity; ankle clonus was sustained, and there was a positive Babinski sign. Abdominal reflexes were absent bilaterally; the cremasteric reflex was present on the right side and absent on the left. All other reflexes were normal. There was no impairment for position, vibration or light touch sensation. There was analgesia for pinprick in the right lower extremity and over the trunk as high as the seventh rib on the right side, the area reaching just to the midline anteriorly and posteriorly. There was a greater degree of sweating on the left side than on the right. Nystagmus was noted on lateral gaze in either direction. Examination otherwise revealed nothing abnormal.

Lumbar puncture, performed the following day, revealed that the spinal fluid was clear and colorless, with normal pressure and manometric readings. There were 2 cells per cubic millimeter and 22 mg. of protein per hundred cubic centimeters. The Wassermann reaction was negative; the colloidal gold curve was 0000000000.

Course.—Two days after admission, the patient complained of pain in the left flank and difficulty in starting urination. Urinalysis and studies of the blood showed nothing significant, and a roentgenogram of the spine revealed no abnormalities. The patient left the hospital about a week after admission, with no essential change in his condition. He was again hospitalized on May 4. He had been catheterized regularly and had some fever, but the urine was not grossly infected. The paralysis had continued to ascend and now involved the left hand severely and the right hand to a lesser extent. The lower limbs were completely paralyzed and flaccid. Reflexes were diminished, and the Babinski sign was absent. The sensory level had ascended to the cervical dermatomes. There were complete loss of sensation below the nipple line, diminution of sensibility for all modalities as high as the eighth cervical segment and impairment of perception of pinprick up to the level of distribution of the trigeminal nerve. The patient was unable to turn over in bed or to breathe while lying

on his face. Priapism was noted, and there was nuchal rigidity with pain on forward flexion. No abnormalities of the cranial nerves were detected. Tympanites developed and became persistent.

Another spinal puncture revealed slightly xanthochromic fluid, with 320 cells, mostly leukocytes, and an increase in protein.

Large bed sores developed, and the patient died on May 21, about six weeks after the onset of symptoms.

Necropsy.—The brain showed no gross abnormalities aside from moderate edema. The spinal cord was removed intact, with the dura unopened. No abnormality was noted in the spinal canal. The dura was slit to expose the cord, the surface of which appeared grossly normal. Transverse section in the cervical region showed normal demarcation of the white and gray matter. The cord was edematous, and the cut surface rolled up. Section in the lower thoracic region disclosed a very soft, pulpy substance, and the gray matter could not be distinguished. The lower segments of the cord were softened. After fixation, sections revealed that the normal markings were obliterated below the midthoracic region.

Microscopic preparations revealed profound alterations within the spinal cord. In the lower thoracic and the lumbar and sacral segments scarcely any recognizable architecture could be made out. No nerve cells were preserved. In cross section, the cord was free from myelin and nerve fibers and presented a host of granule cells loaded with reddish-staining fat in sudan preparations, along with a delicate reticulum of connective tissue. Little gliosis, little

Fig. 6 (case 4).—Sections showing complete loss of form of the spinal cord, with hemorrhage into the parenchyma. Weigert stain; × 4.

inflammatory infiltration and no inflammatory exudate over the meninges was evident. The process was intraspinal in extent. The central canal could usually be made out, but beyond this the tissue showed almost complete destruction. The vessels of the cord showed little change other than proliferation of new ones. The anterior spinal artery was intact in all sections.

The upper thoracic and cervical regions showed much better preservation, except in the myelin preparations, which revealed almost total loss of myelin in the dorsal columns, with large vacuoles in the ventral and ventrolateral regions. Fat-filled granule cells were fairly numerous, appearing chiefly in the dorsal columns. However, the ventral horn cells were also affected, showing rounded outlines, eccentric nuclei and loss of chromatin.

The process seemed to stop short of the medulla, and at the level of the nucleus of the twelfth nerve no myelin degeneration or reaction of any kind could be seen. No abnormality was observed in the pons, midbrain or cortex.

Case 4.—*History.*—O. U., a white woman aged 55, entered the hospital complaining of paralysis of the legs and inability to void. Ten days prior to onset of the present illness she had had an acute infection of the respiratory tract, from which she recovered without apparent incident. On January 22 she noticed that the left hip was numb and then the left leg, and later in the day the left foot became paralyzed. On January 23 she was unable to urinate and the right leg became weak. She entered the hospital on January 25. The history was otherwise unrevealing.

TABLE 4.—*Summary of Cases in Present Series*

Age, Yr.; Sex	History and Onset of Illness	Clinical Observations	Course and Duration	Spinal Fluid	Postmortem Observations
42; female (Negro)	Sinusitis 3 yr. and hypertension 6 yr. Onset with obstipation, weakness of left leg, and then of left arm, with pain, followed by weakness of right leg; involuntary spasms	Weakness of all extremities atrophy; spasticity; hyperreflexia; pyramidal signs; increased threshold for position sense. Nystagmus; conduction deafness on right	After 2 wk. profound hypotonia below waist; sensory level to C 8; areflexia in lower extremities. Ascending urinary infection; decubitus; death 5 mo. after onset	(1) 20 lymphocytes; protein 175 mg. per 100 cc. (2) 3 cells; Pandy reaction +; protein 100 mg. per 100 cc.; Kahn reaction —; colloidal gold curve 4332211100	Cervical portion of cord softened; structure disrupted on left side, white and gray matter destroyed. Vacuolation; mesodermal reaction; necrosis. Vascular hyperplasia. Lymphocytic infiltrations; compound granular corpuscles; nerve cell degeneration
70; female	Pain in chest and right shoulder following strain. Two mo. later, onset with weakness of lower extremities and difficult urination	Weakness of lower extremities; reflexes preserved. Sensory diminution below 3d rib; later, complete flaccid paralysis of lower extremities; areflexia; weakness of upper extremities. Nystagmus; ptosis	Pain in chest and shoulders; paresthesia of extremities; muscular wasting. Death 3 wk. after onset of weakness, 3 mo. after onset of pain	2 cells; Pandy reaction ++++; protein 750 mg. per 100 cc.; Kahn reaction —; colloidal gold curve 5554444320. Pressure normal; manometric block	(Carcinoma simplex of thyroid; possible metastases to kidneys.) Spinal cord softened, maximal in thoracic region. Extensive demyelination; spongy appearance; compound granular cells; nerve cell degeneration. Syringomyelic cavity in thoracic region. Vascular hyperplasia; some thrombosis of small vessels. No inflammation
36; male	Weakness of left lower limb, numbness and tingling of right leg 10 days prior to examination	Weakness of left lower limb, with hyperactive reflexes, clonus and Babinski sign. Absence of abdominal reflexes and of cremasteric reflex on left. Impaired pain perception in right lower extremity and over trunk up to 7th rib level on right side	Ascent of paralysis to involve upper extremities; complete flaccid paralysis of lower limbs, with loss of reflexes; sensory level to cervical dermatomes for all modalities. Tympanites; priapism; nuchal rigidity. Urinary retention; loss of sphincter control; decubitus. Death 6 wk. after onset	(1) Clear, colorless; 2 cells; protein 22 mg. per 100 cc.; Wassermann reaction —. (2) Fluid xanthochromic; 320 cells (leukocytes); protein increased	Cord soft and pulpy from lower thoracic region down; normal markings obliterated; complete destruction of nerve cells, fibers and myelin. Numerous granule cells; little inflammation or gliosis. Proliferation of new vessels; others intact. Cervical segments better preserved; myelin and nerve cell degeneration. No involvement of brain stem or cortex
55; female	Infection of respiratory tract 10 days prior to abrupt onset. Numbness and weakness of left leg; urinary retention; weakness of right leg	Flaccid paralysis of lower extremities, with areflexia; sensory loss to Th 10 or 12	Ascent of paralysis to upper limbs; difficulty in deglutition and respiration; sensory level to clavicles. Death 2 wk. after onset	(1) Fluid yellow; 658 white cells, mostly polymorphonuclears; 439 red cells; protein 176 mg. per 100 cc.; Kahn reaction +; (blood Kahn reaction —); colloidal gold curve 1112311000. (2) Deeply yellow; 32 red cells and 17 white cells (polymorphonuclears); Kahn reaction —; colloidal gold curve 4444332200	Massive destruction of thoracic portion of cord, with herniation; no structures recognizable; necrosis, surrounded by zone of hemorrhage in lower thoracic region. Numerous gitter cells; no inflammation. Vascular hyperplasia; fragmentation of elastica; thromboses

Examination.—The temperature ranged at about 100 F., the pulse rate about 100 and the respiratory rate about 20. The blood pressure was normal.

The cranial nerves were normal.

There was flaccid paralysis of the lower extremities, with loss of tendon reflexes. The lower abdominal reflexes were absent, and the upper ones were intact. Sensory examination revealed a complete loss of sensation extending to the level of the twelfth thoracic segment on the right side and to the tenth thoracic segment on the left side. Lumbar puncture on January 28 revealed hazy, pale yellowish fluid, under a pressure of 125 mm. of water. The total protein was 176 mg. per hundred cubic centimeters; there were 439 red blood cells and 658 white cells per cubic millimeter, with 95 per cent polymorphonuclears. The Kahn reaction was positive, and the colloidal gold curve was 1112311000.

The blood count was normal, and the Wassermann reaction of the blood was negative.

Roentgenograms of the spine and chest revealed nothing significant.

Course.—On February 1 the abdomen was distended and tympanitic. There was extension of the motor involvement to the upper extremities, with weakness of the hands and some difficulty in respiration. Analgesia now extended to the xiphoid cartilage and anesthesia to the umbilicus. All sensation was absent in the lower limbs, which were the seat of flaccid paralysis with areflexia. Lumbar puncture now revealed a deep yellow fluid, with 32 red blood cells and 17 white cells, 90 per cent of which were polymorphonuclears. The Kahn reaction was negative and the colloidal gold curve was 4444332200.

On February 2 there were slight cyanosis, difficulty in swallowing and inability to protrude the tongue. Ascent of the paralysis continued, and on February 4 an area of hyperesthesia, extending to the clavicles, was noted. There was no response to sulfapyridine (2-[paraamino-benzenesulfonamido]-pyridine) therapy, and death occurred on February 5, two weeks after the onset of symptoms referable to the spinal cord.

Necropsy.—Softening of the cord was extensive, with maximal involvement in the thoracic segments. In this region massive central necrosis was seen, with herniation of the substance of the cord through the incised dura. Microscopic preparations through these thoracic segments were so fragmented and distorted that the internal structures were difficult to recognize. A large central infarction with advanced coagulation necrosis, surrounded by a zone of hemorrhage, was seen in the lower thoracic segments. The higher thoracic segments showed somewhat better preserved architecture, but there was uniform cellular destruction, and only a few viable nerve cells remained in one portion of the anterior horn.

In the cervical region, sections revealed still better preservation of structure. Degenerative changes in the anterior horn cells were seen, and there was a pronounced vascular reaction. The latter was widespread throughout the cord and consisted of endothelial swelling of the small vessels, as well as moderate medial and intimal thickening of the larger ones. In many instances there was fragmentation of the elastica in the medium-sized vessels. About a number of the penetrating vessels of the cord there was a coagulated, acellular exudate, which stained deeply with eosin. Many of these vessels were thrombosed. Gitter cells were numerous throughout the areas of softening. No inflammatory reaction was seen, and a glial reaction could not be demonstrated.

Sections of the medulla and pons revealed no frank lesions. Cell stains showed a relatively normal picture, and myelin sheath stains here showed no remarkable degeneration.

COMMENT

A number of observations may be made from the foregoing descriptions. The cases recorded in the present report, as well as those summarized from the literature, fall under two heads: the acute and the subacute or chronic type.

The acute type varies in duration from ten days to three months. The onset is usually abrupt, with flaccid paralysis and complete sensory loss from the start. Pains and paresthesias are sometimes noted. Ascent of sensory and motor impairment may occur over a period of several days, although in a few instances the level remains stationary. An acute febrile course is occasionally seen, but for the most part fever appears with the advent of infection of the urinary tract or terminal infection of the respiratory tract. The spinal fluid in general shows an increase in protein and cells, although occasional dissociation and some normal fluids have been recorded. The course is progressive, without remission, and is invariably fatal. Anatomically, the striking feature is softening of the spinal cord, with

disruption of the normal structure. Destruction includes both the white and the gray matter as a rule, although some authors have described predominant involvement of the white matter. Both the myelin sheaths and the axis-cylinders are generally affected. In some areas a spongy or lacunar appearance is imparted as the result of diffuse demyelination. Cellular reaction is generally not of an inflammatory nature, although in some of the cases reviewed lymphocytic infiltrations were noted, and in a few polymorphonuclears were seen. Compound granular corpuscles are seen in large numbers. The intramedullary blood vessels are generally hyperplastic and sometimes thrombosed, and occasionally hemorrhages are noted.

The subacute or chronic type varies in duration from several months to two years or more. In an impressive number of cases weakness of the lower extremities is at first accompanied by increased tonus and hyperactive or well preserved reflexes, with subsequent change to flaccidity, atrophy and loss of reflexes. Sensory loss, as well as motor impairment, frequently shows ascent, and early sensory dissociation later becomes complete. The prevailing change in the spinal fluid is increase in protein, sometimes with pleocytosis, sometimes without. The pathologic changes include softening, usually maximal in the cervical or the thoracic region. Degeneration involves the white and the gray matter, although some authors have described predominant changes in the gray matter. Fragmentation, vacuolation or frank necrosis of the parenchyma, with homogeneous appearance and failure to stain, are seen. Demyelination, with a spongy appearance, may be noted. Vascular hypertrophy is frequent, the large extramedullary vessels being involved in some cases but the intramedullary vessels being affected more notably, with narrowing of the lumen. Necrosis or degenerative softening is generally most advanced in the neighborhood of the vessels which show most striking hyperplasia. Inflammation is characteristically absent, although not invariably. Occasionally lymphocytic infiltrations are described. Compound granular corpuscles are seen in many areas, and reactive glial changes may be present.

There is no intention here of classifying this general picture as an entity; rather, our purpose is to indicate trends and similarities in a number of diverse cases, some of which may represent the activity of a specific toxic or infectious agent.

It is interesting to note the general disagreement with regard to nomenclature. Among the early authors who criticized the inaccurate use of the term "myelitis" in referring to many different diseases of the spinal cord were Bastian,[38] Singer,[39] Biernacki,[40] Starr,[41] Oppenheim [42] and Henneberg.[43] These authors demonstrated that in many cases a condition designated as myelitis was actually softening due to vascular occlusion, and this view has long been substantiated.

Wilson coined the term "thrombomyelia" to describe the myelomalacias of varying origin. Numerous known precipitating factors have been described, the

38. Bastian, H. C.: Thrombotic Softening of the Spinal Cord as a Cause of So-Called "Acute Myelitis," Lancet **2**:1531 (Nov. 26) 1910.

39. Singer, H. D.: Pathology of So-Called Acute Myelitis, Brain **25**:332, 1902.

40. Biernacki, E.: Myelopathia endarteritica acuta, Deutsche Ztschr. f. Nervenh. **10**: 173, 1897.

41. Starr, M. A.: Organic Nervous Diseases, Philadelphia, Lea Bros. & Co., 1903, chap. 19.

42. Oppenheim, H.: Zum Kapitel der Myelitis, Berl. klin. Wchnschr. **28**:761, 1891; Lehrbuch der Nervenkrankheiten, ed. 7, Berlin, S. Karger, 1923, p. 447.

43. Henneberg, R.: Die Myelitis und die myelitischen Strangerkrankungen, in Lewandowsky, M.: Handbuch der Neurologie, Berlin, Julius Springer, 1911, vol. 2, p. 694.

condition having been recorded as a sequel to influenza,[44] metastatic abscess,[45] Pott's disease,[46] antityphoid [47] and antirabic [48] inoculation, therapy with arsenical [49] and sulfonamide compounds,[50] toxic absorption from malignant tumors,[51] indirect trauma,[52] syphilitic [39] and arteriosclerotic [53] thrombosis, arteriosclerosis of the aorta, with occlusion of intercostal and lumbar arteries,[54] and embolism secondary to bacterial [54] or parasitic infection.[55]

A contributing factor to the lack of uniformity in pathologic observations, and hence classification, may be that bacteria, as well as inflammatory cell infiltrations, can disappear early from true myelitic foci, with little remaining evidence of the inflammatory nature of the lesion. In the case of Cassirer and Lewy,[45a] which was clearly one of metastatic myelitis, changes in the spinal cord were not unlike those noted in some of the cases reviewed in this paper, the lesions in the latter being usually ascribed to some toxic-infectious process or degenerative softening. The experimental work of Lotmar [56] presented further evidence of this fact. Injection of dysentery toxin into rabbits produced necrotic foci in the spinal cord, with degeneration of nerve elements and regressive glial changes, without much evidence of inflammation.

Variability of the inflammatory process is notable in cases of the disease following grip or influenza. Inflammatory changes were negligible in the cases of postinfluenzal myelitis included in our review, but were prominent in the cases described by Spiegal,[44a] Puusepp [44b] and others.

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44. (*a*) Spiegal, O.: Myelitis nach Grippe, Wien. klin. Wchnschr. **32**:907, 1919. (*b*) Puusepp, L.: Akute aufsteigende Myelitis als Komplikation der Influenza, Ztschr. f. d. ges. Neurol. u. Psychiat. **87**:377, 1923.

45. (*a*) Cassirer, R., and Lewy, F. H.: Ein Beitrag zur metastatischen Myelitis, Monatschr. f. Psychiat. u. Neurol. **52**:127, 1922. (*b*) Henneberg: Ascendierende, infiltrative Myelitis nach Erysipel, Zentralbl. f. d. ges. Neurol. u. Psychiat. **28**:240, 1922.

46. Hassin, G. B.: Histopathological Changes in Five Cases of Myelitis, M. Rec. **90**:619 (Oct. 17) 1916.

47. Divry; Moreau, M., and Ory: Myélomalacie à évolution foudroyante, survenue après une vaccination antityphique, J. de neurol. et de psychiat. **29**:369 (June) 1929.

48. Cacciapuoti, G. B.: Trombo-arterite midollare con sindrome di Brown-Séquard da vaccinazione antirabbica, Cervello **12**:189 (May) 1933.

49. Glaser, M. A.; Imerman, C. P., and Imerman, S. W.: So-Called Hemorrhagic Encephalitis and Myelitis Secondary to Intravenous Arsphenamines, Am. J. M. Sc. **189**:64 (Jan.) 1935. Mingazzini, G.: Klinischer und pathologisch-anatomischer Beitrag zum Studium der Myelitis haemorrhagica postsalvarsanica, Deutsche Ztschr. f. Nervenh. **104**:1 (June) 1928.

50. Schubert, M.: Todesfall infolge Rückenmarkserweichung nach Uliron (Kombinationsschädigung), Dermat. Wchnschr. **107**:1361 (Nov. 19) 1938. Santo, E.: Ueber eine schwere Erkrankung des Rückenmarkes nach Ulironbehandlung einer Gonorrhoe, Frankfurt. Ztschr. f. Path. **53**:105, 1939. Germain, A., and Picard, P.: Myélite nécrotique subaiguë consécutive a l'injection intrarachidienne de 693 en solution sodique dans un cas de méningite cérébro-spinale, Bull. et mém. Soc. méd. d. hôp. de Paris **56**:670 (Nov. 25) 1940.

51. Spiller, W. G.: Rapidly Developing Paraplegia Associated with Carcinoma, Arch. Neurol. & Psychiat. **13**:471 (April) 1925.

52. Grinker and Guy.[53] Cadwalader.[59]

53. Zeitlin, H., and Lichtenstein, B. W.: Occlusion of the Anterior Spinal Artery, Arch. Neurol. & Psychiat. **36**:96 (July) 1936.

54. Janota, O., and Jedlička, V.: Přisěvek ke kapitole o myelomalaciich, Časop. lék. česk. **74**:681 (June 21) 1935.

55. Rizzi, I.: Degenerative Myelitis Due to Echinococcus Embolism, Riv. di pat. nerv. **45**:397 (March) 1935. Dévé, F.; Lhermitte, J., and Trelles, J. O.: Myélomalacie, paralysie extenso-progressive secondaire à l'échinococcose intrarachidienne lombaire, Rev. neurol. **1**:623 (April) 1932.

56. Lotmar, F.: Beiträge zur Histologie der akuten Myelitis und Encephalitis, sowie verwandter Prozesse; auf Grund von Versuchen mit Dysenterietoxin, in Nissl, F., and Alzheimer, A.: Histologische und histopathologische Arbeiten über die Grosshirnrinde, Jena, G. Fischer, 1913, vol. 6, p. 248.

Some disagreement has recently arisen regarding the term "necrosis," which has been applied rather freely in the cases included in the present review. Hassin [57] differentiated softening and necrosis. He maintained that a necrotic area should be amorphous, devoid of blood vessels or any other tissue elements and incapable of staining. Other investigators have implied a more general process, characterized by destruction of the essential functioning elements of the tissue.

With regard to the etiologic factors and the pathogenesis, little can be added here which has not already been considered. In the cases reported the age incidence was predominantly between the third and the fifth decade, and the cases were almost equally distributed between the sexes. The history of a previous illness was in most cases questionably related to the onset of involvement of the spinal cord. In most instances no preceding illness was noted. In a few cases the presence of hypertension or albuminuria had been known. Lead colic had occurred in 1 of the cases of Foix and Alajouanine, and Moersch and Kernohan, in the investigation of their cases, made determinations of lead, with negative results. Gout was present in 1 case. In 3 cases the onset was associated with or shortly followed pregnancy and childbirth or abortion. In a relatively large number of cases (6) the disease occurred after infections of the respiratory tract, namely, grip or influenza. (Excluded from this study are the numerous cases of unquestioned postinfluenzal myelitis.) A known bacterial infection or local abscess preceded the onset of spinal symptoms in a small number of cases, and fever and chills without known infection, in an additional few. Direct trauma to the back, or indirect trauma by strain, preceded spinal symptoms by varying intervals in 5 of the cases included in this review. No evident vascular occlusion was noted in any of these cases. On the other hand, strain or indirect trauma caused softening and subsequent thrombosis in the cases of Grinker and Guy [58] and Spiller (cited by Cadwalader [59]). It is possible that trauma may cause momentary vascular spasm or constriction, resulting in ischemic softening in one instance or actual thrombosis with softening in another.

Malignant tumor was discovered, or had preexisted, in some other organ in the cases of Nonne, Juba, Feindel, d'Antona and Moersch and Kernohan (case 3) and in our case 3. In Nonne's case there were metastases to the vertebral bodies, but the interspaces were intact and the meninges and cord free from metastases. The transmission of some toxic substance from the malignant tumor, by way of the blood stream to the spinal cord, has been suggested. There is no definite evidence for this assumption, but the possibility remains.

On the whole, the toxic and infectious factors seem more prominent than the degenerative elements in the cases reviewed. This has been the impression of many of the authors reporting these cases. It has frequently been remarked that parenchymal destruction has seemed most prominent in areas showing maximal vascular hyperplasia. Indeed, it has been the usual observation that little or no hypertrophy of blood vessels was seen outside these areas. One would expect a degenerative reaction to be more diffuse in the spinal cord, as well as in other viscera. On the other hand, a toxi-infectious agent reaching the spinal cord by hematogenous transmission might well cause a destructive process in the paren-

57. Hassin, G. B.: On Softening of Central Nerve Tissues, J. Neuropath. & Exper. Neurol. **1**:200 (April) 1942.

58. Grinker, R. R., and Guy, C. C.: Sprain of the Cervical Spine Causing Thrombosis of the Anterior Spinal Artery, J. A. M. A. **88**:1140 (April 9) 1927.

59. Cadwalader, W. B.: Observations on the Character of the Onset of Spinal Paralysis with Reference to the Significance of the Apoplectiform Type of Onset in Contrast to the Slow Progressive Development of Paralysis, Arch. Neurol. & Psychiat. **6**:541 (Nov.) 1921.

chyma and reactive hyperplasia of the blood vessels. It was the opinion stated by Foix and Alajouanine that such a process had in their cases affected the media of the vessels and the parenchyma of the cord simultaneously. In no subsequent case was there the extreme hypertrophy of the large extramedullary vessels, which were described by these authors as having an "onion skin" appearance. In case 2 of our series hypertrophy of these vessels was prominent (fig. 2), but not as remarkable as that noted by the French authors. Intramedullary vascular hyperplasia was seen rather consistently.

The occurrence of spasticity in the early phases in some cases, followed by flaccidity and loss of reflexes, is deserving of mention. It is likely that the early involvement of the white matter, with later destruction of the gray matter, accounts for this clinical feature.

SUMMARY

Necrosis or softening of the spinal cord has been described by numerous observers. Aside from the cases in which the cause was known to be thrombotic, traumatic, toxic or infectious, a general group may be considered in which the etiologic factors are obscure. These have been recorded under various headings, such as acute or subacute necrotic myelitis, progressive necrosis of the spinal cord, myelomalacia and myelodegeneration. There is little agreement regarding the etiologic factors or the nature of the pathologic changes.

The literature is reviewed, and 4 case studies are presented to indicate the general clinical pictures and the predominant pathologic changes.

It is suggested that in many of the cases reviewed, as well as in those presented, toxi-infectious causative factors and tissue reactions appear to exist. No specific agent has as yet been identified, but the possibility of its existence should be considered.

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INCLUSION BODIES AND LATE FATE OF GANGLION CELLS IN INFANTILE AMAUROTIC FAMILY IDIOCY

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The changes in the ganglion cells in infantile amaurotic family idiocy are well known through the studies of Sachs,[1] Schaffer,[2] Bielschowsky[3] and Spielmeyer,[4] to mention only the leading investigators in this field. There are lacking, however, investigations concerned with the later fate of the altered ganglion cells in cases of infantile amaurotic family idiocy of long duration, as are studies of inclusion bodies, which are obviously related to the late changes in the ganglion cells. Finally it would be desirable to establish the relationship between the pathologic changes and the clinical signs, since these signs cannot be explained exclusively by the alterations in the ganglion cells, which are affected throughout the entire neuraxis.

For all these reasons the following cases were studied.

REPORT OF CASES

CHEMICAL STUDY

CASE 1.—L. S., a 3 year old boy, was admitted to the Jewish Hospital of Brooklyn, service of Dr. Leo Davidoff, on Dec. 12, 1941 and died on December 24.

Family History.—The maternal grandmother had a retroperitoneal sarcoma; the paternal grandfather, diabetes. There was no other familial disease in the family, which was traced back to the great-great-grandparents on each side. The patient had a brother with a condition diagnosed as Tay-Sachs disease in 1936 (Dr. Bernard Sachs); this brother was admitted to the Neurological Institute of New York on Feb. 13, 1935 and was dismissed on March 26 of the same year, with the diagnosis of amaurotic family idiocy. He died at the age of 15 months, of pneumonia.

Illness on Admission.—The patient appeared to be normal until the age of 3 months, when it was noted that he was irritable and was startled easily. Since this reminded the

This study was aided by a grant from the Rockefeller Foundation.

Dr. Leo Davidoff put at my disposal the history in case 1, and Dr. Max Lederer furnished the pathologic specimens.

This paper was begun in collaboration with Dr. Alexander Ellman, of the Brooklyn Jewish Hospital, who, however, had to discontinue the work because of service in the Army.

From the Department of Neurology, Columbia University College of Physicians and Surgeons; the Jewish Hospital of Brooklyn, and the Research Laboratory for Neuropathology, Montefiore Hospital.

1. Sachs, B.: (*a*) On Arrested Cerebral Development with Special Reference to Its Cortical Pathology, J. Nerv. & Ment. Dis. **14**:541, 1887; (*b*) On Amaurotic Family Idiocy: A Disease Chiefly of the Gray Matter of the Central Nervous System, ibid. **30**:1, 1903; (*c*) Pressing Problem Concerning Amaurotic Family Idiocy in Its Relation to Other Hereditary and Familial Diseases, in Internationaler Neurologen-Kongress, Copenhagen, Einar Nunksgaard, 1939.

2. Schaffer, K.: Ueber das morphologische Wesen und die Histopathologie der hereditärsystematischen Nervenkrankheiten, Berlin, Julius Springer, 1926; Die pathologischen Reactionsformen des Neurons, Hirnpath. Beitr. **18**:37-42, 1938.

3. Bielschowsky, M.: Ueber spätinfantile familiäre amaurotische Idiotie mit Kleinhirnsymptomen, Deutsche Ztschr. f. Nervenh. **50**:7-29, 1914.

4. Spielmeyer, W.: Klinische und anatomische Untersuchungen über eine besondere Form familiärer amaurotischer Idiotie, in Nissl, F., and Alzheimer, A.: Histologie und Histopathologie. Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1908, vol. 2, pp. 193-251.

mother of the sibling, the infant was given a thorough examination. Cherry red macular spots were noted in both eyes. The child was sent to the New York Hospital. After three weeks there amebic dysentery developed, from which he recovered in six months. In February 1940 he was again sent to the New York Hospital but was discharged in two weeks because of an infection of the upper respiratory tract. In September 1940 the child contracted pneumonia, from which he recovered in ten days. A few months after this it was noted that his head appeared to be larger than normal. Since then the head had increased steadily in size. During the three months before admission the patient lost consciousness three to four times a day for periods lasting up to one and a half minutes. During these periods the mother frequently saw the extremities shake. The patient was never able to sit up. He was able to move all his extremities, but the legs less than the arms.

Physical Examination.—The child was well nourished and did not look acutely ill. He appeared to be hydrocephalic. He was quiet and showed no interest in his surroundings. When he was startled there were tonic and clonic convulsions of the arms and legs. He maintained a position in which there were pronounced eversion of the hips, flexion of the knees and plantar flexion of the feet. He moved his arms spontaneously and the lower extremities only when disturbed. There was marked hypertonicity of all the extremities. The pupils did not react to light. The eyes did not follow a moving light. They blinked when a threatening move was made close to them. The head measured 58 cm. in circumference. The anterior fontanel admitted 1 finger and was shifted 2 cm. to the left of the midline. There was a corneal scar of the left eye. The disks were clear but atrophic. Cherry red macular spots were seen in both eyes.

Examination of the chest revealed Harrison's groove and coarse, bubbling bronchial rales.

Course in the Hospital.—The temperature rose to 104 F.; the respiratory rate increased to 56 a minute, and breathing became labored. Sulfadiazine (2-[paraaminobenzenesulfonamido]-pyridine) was given by stomach tube, and the patient was placed in an oxygen tent. He died on December 24, at 11:15 p. m.

Laboratory Data.—The blood count, made on December 12, revealed 74 per cent hemoglobin, 4,900,000 red cells and 9,400 white cells, with 59 per cent polymorphonuclear leukocytes, 38 per cent lymphocytes and 3 per cent monocytes. The number of platelets was adequate.

Urinalysis revealed acidity, a specific gravity of 1.008 and a faint trace of albumin.

Simultaneous lumbar and ventricular punctures, made on December 16, revealed no block. The colloidal gold curve showed no alteration. On December 17 the Kahn reaction, and on December 20 the Wassermann reaction, were negative.

Diagnosis.—The clinical diagnosis was Tay-Sachs disease, bronchopneumonia and hydrocephalus. The duration of the illness was two years and nine months.

The primary anatomic diagnosis was bilateral focal pneumonia, with Staphylococcus aureus and hemolytic streptococcus; bronchitis; macrocephalus with sclerosis (Tay-Sachs disease); thrombosis of the dural and cerebral veins; subarachnoid hemorrhage; fatty changes in the liver, and necrosis of the thymus gland.

Subsidiary changes were hydropic alterations in the adrenal glands and emphysema.

Case 2.—An 18 month old Jewish girl was examined by Dr. Bernard Sachs, Dr. Louis Hausman and me (in private consultation). The family history was without significance except for a case of schizophrenia in the father's family; there was no consanguinity, and both parents were healthy. According to the parents, the disease began at the age of 9 months, but sight was disturbed some time earlier. There was general weakness; later blindness occurred. Ophthalmoscopic examination revealed optic nerve atrophy and cherry red macular spots. The child was lying in bed with the arms in slight flexion, the legs abducted and everted at the hips, the knees bent and the feet in the equinovarus position. There were hyperacusis and hyperpathia. The tendon reflexes were not exaggerated; there were no pathologic reflexes, but the abdominal reflexes were absent. No laboratory data were available except those from urinalysis, which were normal.

The child died of pneumonia at the age of 18 months.

The diagnosis was infantile amaurotic family idiocy. The duration of the disease was nine months.

Case 3.—The case was one of Niemann-Pick disease with amaurotic family idiocy. The duration of the illness was nine months. This case was studied in collaboration with Dr. E. Epstein and was prepared for publication at the Neurological Institute of the University of Vienna in 1935.

CASE 4.—The case was one of amaurotic idiocy. The cortex has been described in a paper by Inaba.[5]

PATHOLOGIC STUDIES

CASE 1.—*Spinal Ganglia.*—In hematoxylin and eosin preparations the swollen cells showed a fine, dark blue dust around the nucleus, which was usually eccentric, while the cell body was bright red and contained very small granules. Occasionally the cell body appeared honeycombed, with vacuoles of varying sizes. In such a cell the cell body seemed to be represented by vacuoles of different sizes surrounded by plasma, since there were no red-staining granules. In some cells there were tigroid bodies around the nucleus; in others, neither tigroid bodies nor debris was evident. Occasionally the nucleus showed homogeneous shrinking. In some cells the debris was coagulated, while the nucleus formed a homogeneous, dark blue mass (fig. 1). Later the altered nucleus became coagulated with the homogeneous debris, whereas the rest of the cell body remained unchanged and took a reddish stain. In some cells this remnant of the cell body was also altered and stained pale blue, without presenting any structure. Finally, both these amorphous masses appeared coagulated. At this stage the cell was represented by a shrunken, amorphous mass, which stained blue with hematoxylin

Fig. 1 (case 1).—Inclusion bodies from a spinal ganglion, showing one cell with vacuole and another resembling an amyloid body. Hematoxylin and eosin stain.

and resembled a cell only in shape. Some cells had completely disappeared, and the remaining gaps were filled with capsule cells.

Some of the spinal ganglion cells contained inclusion bodies (fig. 1). They were seen in a reddish ground substance, stained somewhat brighter red, as though some material was extracted, consisted of small globules and gave the impression that they were situated within a vacuole, apparently as a result of shrinkage. Some, however, were dark blue, like amyloid bodies (fig. 1, ventral cell). The picture was similar in Nissl preparations, in which the inclusion bodies stained pale blue.

With silver impregnation after the Bodian stain (fig. 2) two networks were stained: an interstitial one, in part regular, with very fine strands, and in part presenting thick and irregular strands; and a superficial network formed by fibrils which crossed each other and were intermingled with very fine sprouts of axons. The nucleus and the debris were black; the coagulated masses, grayish. The inclusion bodies were recognizable by a faint gray tint. The destruction of the ganglion cells caused an increase of capsule cells which filled the empty spaces.

5. Inaba, C.: Zur Frage der amaurotischen Idiotie, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **30**:360-366, 1928.

In sudan III preparations the cell bodies appeared light orange; they did not stain with osmic acid. In preparations stained with nile blue sulfate fine and coarse granules, as well as the inclusion bodies appeared darker blue than most of the finest granules.

The iron hematoxylin stain revealed a very fine black network in the inclusion bodies, with grayish granules within this network. Some granules in the cell bodies stained black.

Spinal Cord.—All the cells of the spinal cord were swollen (figs. 3, 4 and 5). Those of the posterior horn were less damaged than those of the anterior horn. In the smaller cells, such as those in Rolando's gelatinous substance, there was no debris, whereas the larger cells, particularly those in Clarke's column, presented the typical aspect of cells in infantile amaurotic family idiocy. Secondary changes were seen especially in the cells of the anterior horn. There were inclusion bodies (fig. 3), as well as transformation of the cell contents into amorphous masses (fig. 4). In addition to the amorphous masses formed within the cell,

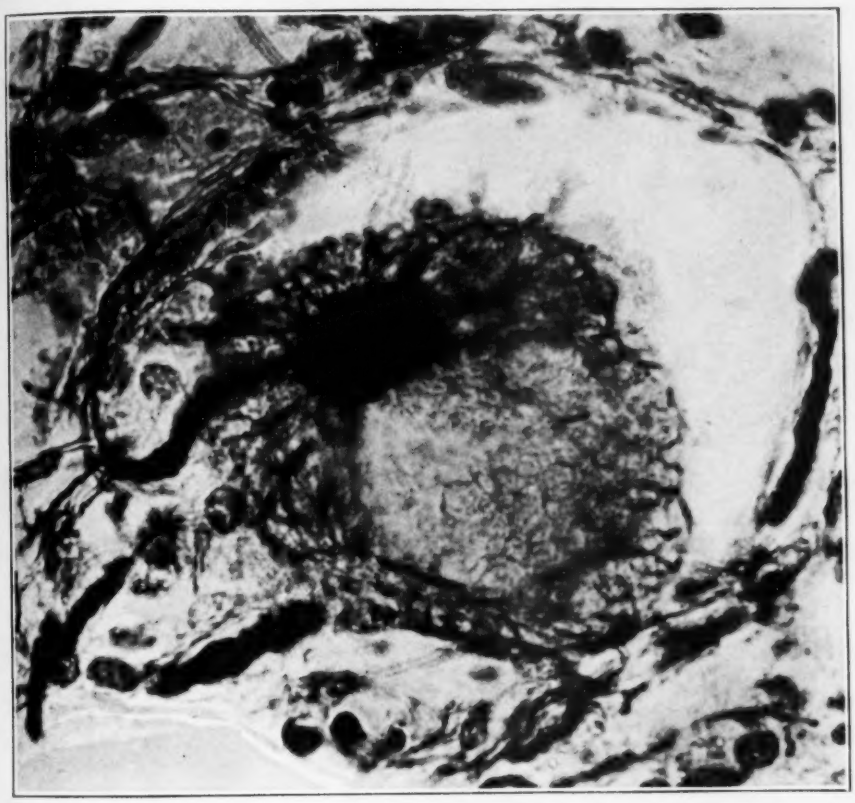

Fig. 2 (case 1).—Spinal ganglion, showing a superficial and an interstitial network; in the right upper corner of the cell is an argentophobic inclusion body. Bodian stain.

there were two other formations of such material. The first was easily recognizable by globular, sometimes irregular, masses arising from swollen axons (fig. 5); such formations are of frequent occurrence in cases of amaurotic idiocy. The second type of amorphous material lay apparently free in the tissue (fig. 6), without connection with ganglion cells or axons. All these amorphous masses stained the same color—pale blue with hematoxylin and grayish black with silver. In single cells there were sudanophilic granules (neutral fat[?]); in other cells single vacuoles or fat droplets of various sizes (fig. 4) were apparent.

Cerebellum.—Lack of ganglion cells was apparent in all layers. They were replaced by numerous scattered, round or pear-shaped bodies, the nature of which was easily revealed. Some of these globular bodies were remnants of swollen axons; others were compound granular cells, which stained black with silver, like the globules. A third type was seen in the molecular layer within dendrites of damaged Purkinje cells (fig. 7), obviously inclusion

Fig. 3 (case 1).—Inclusion body in an anterior horn cell. Hematoxylin and eosin stain.

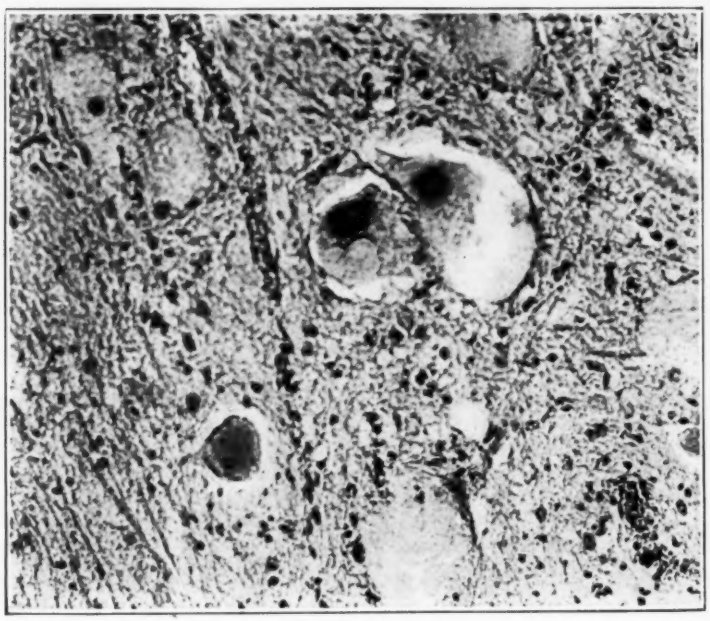

Fig. 4 (case 1).—Amorphous ganglion cell in the lower portion of the photograph; fat droplets of various sizes in the cell above it. Bodian stain.

bodies which had been partly liberated by the destruction of these cells. The dentate nucleus (fig. 8) was severely damaged. Inclusion bodies, as well as shrunken, homogeneous cells, were present, in addition to the well known lipoidosis. There was an increase in the glia, indicating destruction of cells. Axons were scanty, but a significant lack of myelin sheaths was not recognizable.

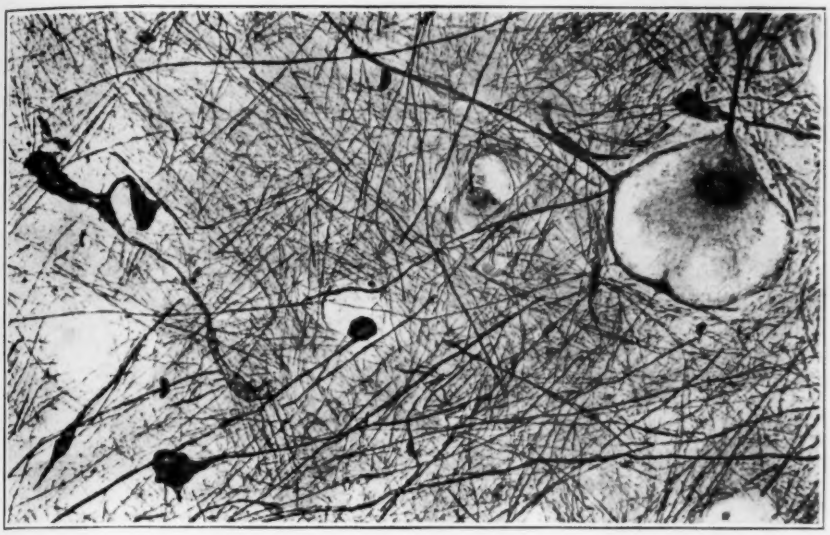

Fig. 5 (case 1).—Swollen cells from the anterior horn, with swollen axons. Bodian stain.

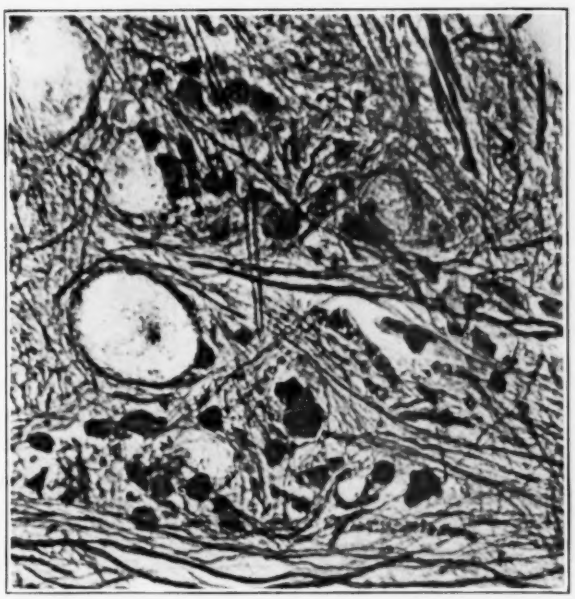

Fig. 6 (case 2).—Amorphous masses free in the tissues; swelling of axons. Bodian stain.

Cerebral Cortex.—All the cortical cells revealed a typical change. The Schaffer stain revealed that many of the ganglion cells were filled with lecithinophilic granules; others were scantily filled, and the ground substance stained reddish with picrofuchsin (fuchsinophilic). In sudan-stained sections the ground substance was bright orange.

Fig. 7 (case 1).—Severely degenerated Purkinje cell, with three inclusion bodies in the dendrites. Bodian stain.

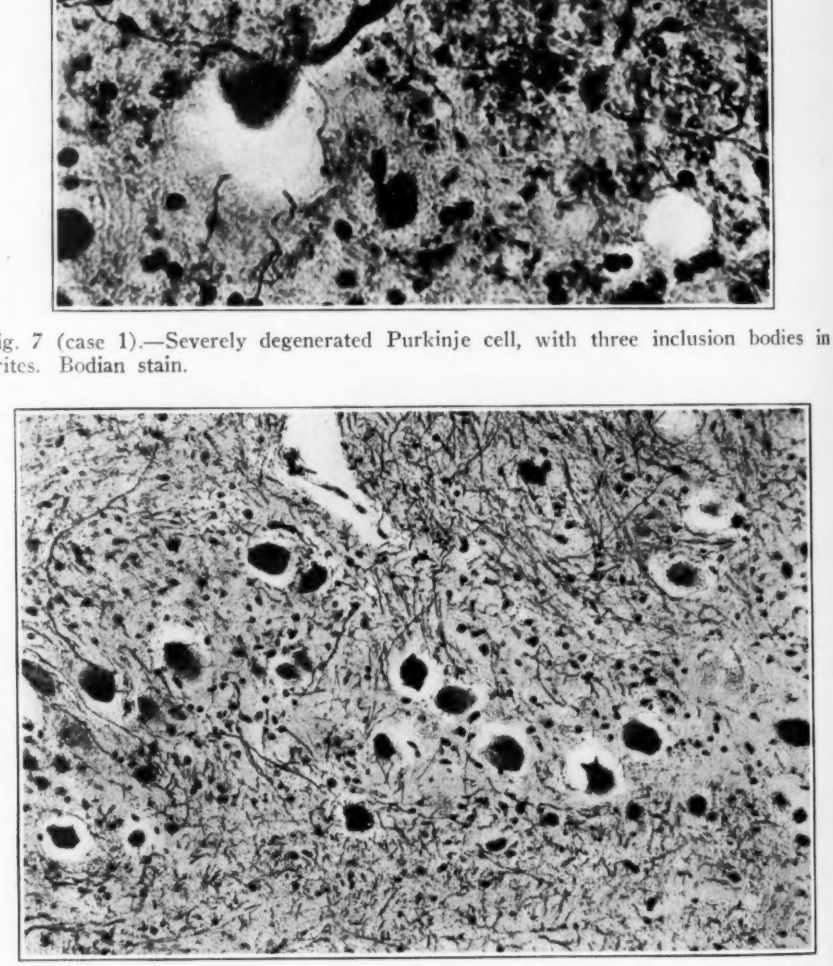

Fig. 8 (case 1).—Section from the dentate nucleus, showing precipitations (left) and destruction of cells (right). Bodian stain.

CASE 2.—While all the cells were degenerated, as in a typical case of infantile amaurotic family idiocy, most of the alterations in the cells described in case 1 were absent. There were only a few extracellular globules and irregular amorphous masses at the boundaries of the anterior horn (fig. 6). They originated partly from swollen axons, and some did not show any relation to surrounding structures.

CASE 3.—The cells in this case of Pick-Niemann disease were filled with hematoxylinophilic bodies; inclusion bodies were absent. In Bielschowsky preparations only the fibrils were impregnated; the cell contents remained unstained.

CASE 4.—All the cells were swollen, but no inclusion bodies or amorphous masses were observed.

COMMENT

The cell changes in cases of infantile amaurotic family idiocy obviously begin with swelling of the cell body, which may be of extreme degree. Closely associated with the cellular swelling are disintegration of the tigroid substance and the simultaneous appearance of fatty substances. The difference in these substances in the various forms of amaurotic family idiocy (infantile, late infantile, juvenile, adult and Pick-Niemann) is well known. The fat in infantile amaurotic family idiocy, as in Pick-Niemann disease, is hematoxylinophilic, but in the former it is not a phosphatide; in the late infantile form the hematoxylinophilic granules disappear, to be replaced to an increasing degree by sudanophilic and osmophilic granules. In cases of the longer-lasting infantile form as in case 1 in the present series, sudanophilic and osmophilic granules are seen, in addition to the hematoxylinophilic granules. Von Sántha [6] claimed that in these longer-lasting forms the hematoxylinophilic granules, indicating the presence of prelipoids or phosphatides, disappear, and the occurrence of light orange–stained droplets then indicates the transformation of the granules into fat, approaching neutral fat. The same change is seen in case 1. In this case, there was in addition, a transformation of this fat partly or entirely to form inclusion bodies or amorphous masses, which led to the death of the cell.

The inclusion bodies in amaurotic family idiocy are of great interest. First described by Bielschowsky [3] as black bodies with clear centers occurring in the dendrite of a Purkinje cell, they were later observed by other authors. One may agree with Bielschowsky that these inclusion bodies do not belong to the pathologic picture of amaurotic family idiocy. It is questionable whether the globules described by Schob [7] correspond to these inclusion bodies. He observed them in the cells of the brain stem, where they stained bluish green with cresyl violet. Since in many cells there were fat droplets of different sizes and shapes, it is possible that Schob's granules were fat droplets. An accurate description of the inclusion bodies in cases of amaurotic family idiocy was given by Hassin.[8] He noted them inside vacuoles in different regions (nucleus ruber; substantia nigra). But in the illustrations some of them are seen to be argentophilic (black); others do not stain with silver or show only a grayish tint. Since the consistency of the inclusion bodies is different from that of the surroundings, occasional shrinkage

6. von Sántha, K.: (*a*) Ueber drei reine, von Niemann-Pickscher Krankheit verschonte Fälle von amaurotischer Idiotie, Arch. f. Psychiat. **93**:675-766, 1931; (*b*) Neuer Beitrag zur Histopathologie der Tay-Sachs-Schafferschen Krankheit, ibid. **86**:665-676, 1929.

7. Schob, F.: Zur pathologischen Anatomie der juvenilen Form der amaurotischen Idiotie, Ztschr. f. d. ges. Neurol. u. Psychiat. **10**:303-324, 1912.

8. Hassin, G. B.: A Case of Amaurotic Family Idiocy: Late Infantile Type (Bielschowsky) with Clinical Picture of Decerebrate Rigidity, Arch. Neurol. & Psychiat. **16**:708-727 (Dec.) 1926.

may occur, as in case 1 in the present series, and the whole inclusion body may thus be removed, with a resulting empty vacuole on the slide. This is probably the explanation of some of the single vacuoles seen in sections in case 1.

Credit is due to Liebers [9] for having been the first to attempt differentiation of the inclusion bodies by various staining methods. In his case amaurotic family idiocy was associated with myoclonus epilepsy, as in my case 1, but not to so pronounced a degree. The inclusion bodies, which were seen in the globus pallidus, the optic thalamus, the dentate nucleus and the nucleus ruber, resembled amyloid bodies; they were acidophilic, lecithinophilic or lipoidophilic, whereas stains for glycogen gave negative results. Somoza [10] described inclusion bodies in Purkinje cells as second nuclei, whereas von Sántha,[6] after thorough investigation, noted inclusion bodies throughout the nervous system in 3 cases of infantile amaurotic family idiocy. He described greatly enlarged cells containing only argentophilic bodies, with the nuclei pressed to the periphery. It is significant that he saw fibrils entering these bodies and that occasionally from the borders of the inclusion bodies silver-stained rays ran into the surrounding tissue.

In the present case there were inclusion bodies which reduced silver in Bielschowsky preparations, as well as inclusion bodies which did not reduce silver. Thus, there were two kinds of inclusion bodies: argentophilic and argentophobic. Both kinds stained almost equally well with other dyes. With hematoxylin and eosin or with fuchsin they stained red, or occasionally reddish blue; in Nissl preparations they were pale blue. The argentophobic bodies showed a slight affinity for hematoxylin, perhaps also for nile blue sulfate, but they did not stain with osmic acid or scarlet red.

Most investigators have held these inclusion bodies to be amyloid bodies because of their similarity to amyloid bodies in the brain. Hassin [8] claimed that they were colloidal substances, "though morphologically they, in some instances, much resembled amyloid bodies and chemically lipoids. Yet they were not affected by such chemicals as alcohol, xylene and ether."

It is impossible to discuss the origin of the inclusion bodies without considering the entire cell process in later stages. The two substances within the cell, namely, (1) the nucleus and the debris around it, chiefly protein, and (2) a fat mixture filling out the bulk of the cell, are changed in the later stages. The nucleus and the debris form a homogeneous mass which stains bluish black with hematoxylin, but the lipoids also become homogeneous, and their color changes from red to blue in hematoxylin and eosin preparations. Both of these substances then coagulate and form an amorphous mass, which stains grayish black in silver preparations and pale blue in hematoxylin and eosin sections. Occasionally one sees in a cell the nucleus only changed into a homogeneous mass, which stains black with silver. Thus, proteins, as well as lipoids, may finally stain black with silver.

In a recent paper I [11] described black granules in ganglion cells in cases of amaurotic family idiocy (silver reduction) and suggested that there is a process of dissolution in the cell in the course of which the tight linkage of protein and lipoids may be dissolved, with production of granules which stain black with silver.

9. Liebers, M.: Zur Histopathologie der amaurotischen Idiotie und Myoklonusepilepsie, Ztschr. f. d. ges. Neurol. u. Psychiat. **111**:465-484, 1927.

10. Somoza: Ueber eigenartige zweikernige Purkinjezellen bei der infantilen amaurotischen Idiotie, cited by von Sántha.[6]

11. Marburg, O.: Studies on the Pathology and Pathogenesis of Amaurotic Family Idiocy, Am. J. Ment. Deficiency **46**:312-322, 1942.

My later investigations [12] showed that the presence of protein is not necessary for the reaction because unsaturated fat also stains black with silver.

To study this problem more accurately, I [13] proceeded as follows: An ammoniacal solution of silver, as used in Bielschowsky's method, was added to a small amount each of an unsaturated fat, a neutral fat and lecithin; no reaction occurred. The addition of calcium phosphate resulted in no reaction, and the only change on addition of a solution of ferric ammonium sulfate was a precipitation of reddish corpuscles. Then a drop of solution of formaldehyde U. S. P. was added to the three test fats in order to reduce the silver; the reduction occurred first in the unsaturated fat and later in the neutral fat, while lecithin inhibited prompt reduction. The result was the same on addition of calcium phosphate. The same experiment performed on a glass slide showed the entrance of silver into the unsaturated fat, whereas in the case of neutral fat silver accumulated around the droplets. Furthermore, a fat droplet to which calcium phosphate was added stained with hematoxylin; it showed a concentric arrangement of dye, the outer ring being dark bluish, the inner ring bluish red and the innermost part almost red. Iodine added to the three test fats did not change the color, but a mixture of iodine and calcium phosphate, which is brownish, kept its color when fat was added.

Since the similarity of the inclusion bodies to amyloid bodies has been emphasized by almost all neuropathologists, the question arises what role fat plays in the formation of the inclusion bodies.

Obersteiner [14] described fat droplets in glia cells, which stained brownish black with osmic acid, the rest of the section remaining unstained. These droplets coagulate and then lose their affinity for osmic acid; they form homogeneous, sometimes concentrically arranged, bodies, which stain blue with hematoxylin. I saw them in hematoxylin and eosin preparations, being reddish in the early stages and later blue, while with the Bielschowsky method they stained black, like the inclusion bodies described by Hassin.[8] Similar observations were mentioned by Casamajor.[15] Thus, these bodies consist of fatty substances, so-called prelipoids, as suggested by von Sántha,[6] or to a greater degree of unsaturated fat, as I [12] suggested.

Waelsch suggested that the nature of the fatty acids in lipoids may influence their properties so that they show the characteristics sometimes of a prelipoid and sometimes of unsaturated fat. Thus the nature of the fatty acids may change, together with the staining abilities of the respective cells.

In this connection one is reminded of the "brain sand" bodies (corpora arenacea, or psammous bodies). Investigations by Yoshimura,[16] Windholz [17] and me [18] revealed the fact that the choroid plexus contains neutral fat intracellularly as well as extracellularly. Windholz [17] assumed that this fat was the basis of the formation of the sand bodies, which stain first reddish with hematoxylin and eosin and later blue, the reaction obviously depending on the calcium content. It may be recalled

12. Marburg, O.: Studies in the Pathology and Pathogenesis of Multiple Sclerosis, with Special Reference to Phlebothrombosis and Guiraud's Bodies, J. Neuropath. & Exper. Neurol. **1**:3-13, 1942.

13. Marburg, footnotes 11 and 12.

14. Obersteiner, H.: Zur Histologie der Gliazellen in der Molecularschichte der Grosshirnrinde, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **7**:300-316, 1900.

15. Casamajor, L.: Zur Histochemie der Ganglienzellen der menschlichen Hirnrinde, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **18**:101-110, 1910.

16. Yoshimura, K.: Das histochemische Verhalten des menschlichen Plexus chorioideus, zugleich ein Beitrag zur Frage der Plexussekretion, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **18**:1-12, 1910.

17. Windholz, F.: Konkrementstudien am Plexus chorioideus, Verhandl. d. deutsch. path. Gesellsch. **23**:296-301, 1926; Die Lipoide des menschlichen Adergeflechts, ibid. **25**:353-357, 1930.

18. Marburg, O.: Hydrocephalus, New York, Oskar Piest, 1940.

here that Hofmeister [19] suggested that in case of cleavage of fat the liberated fatty acids are effective as *Kalkfänger* ("calcium binders"). The concentric or the radial arrangement of the sand bodies is seen with fatty substances or mucin, as is well known in general pathologic studies.[20]

Thus, one might well explain the presence of the inclusion bodies as the result of a process similar to that producing the brain sand and the amyloid bodies, developed on the basis of some kind of fat; their differences in silver-reducing ability may be due, as mentioned previously, to the presence of different fatty acids. The globules and amorphous masses free within the tissue still remain to be explained. In infantile amaurotic family idiocy these globules and irregular amorphous masses are formed by swollen axons, and they finally accept the same shape, size and color as the inclusion bodies within the cells. In this respect fat plays a role similar to that of inclusion bodies within the cells. This fat originates from broken myelin sheaths, and finally these extracellular, axon-developed bodies may approach the pattern of real inclusion bodies. Since in the cases reported by von Sántha [6] fibrils entered into the inclusion bodies within the cells, the possibility cannot be excluded that some of the inclusion bodies take their origin from axons or fibrils, especially as one occasionally sees in cases of amaurotic idiocy a swelling of intracellular fibrils like that in Alzheimer's disease. Another explanation is that given by Alzheimer [21] and Stürmer,[22] that amyloid bodies are formed in free tissue fluid by precipitation. This possibility cannot be excluded in cases 1 and 2. These bodies lie within the boundaries of the gray matter. In addition to the glia cells and axons, fat lies partly free in the tissue or in histiocytes near blood vessels. Though it was impossible to determine the origin of all these inclusion bodies, some of them may well have been formed by precipitation in the tissue, as Stürmer [22] suggested.

Thus, there are three possible ways of explaining the formation of inclusion bodies or amorphous masses in amaurotic family idiocy. The argentophobic inclusion bodies within the cells take their origin from a fatty substance, whereas it is not absolutely certain that this is true for the argentophilic bodies. It seems likely, however, with regard to the formation of amyloid bodies in glia cells. This circumscribed process can affect the whole cell, so that large amorphous masses are formed by the entrance of calcium, iron, glycogen or even protein. The kind of fatty mother substance and the amount of the entering material obviously influence the character of the inclusion bodies. These bodies indicate a change in cell metabolism—some kind of saponification, which is possible within ganglion cells as well as outside.

The significance of inclusion bodies in general is doubtful, for Lewy [23] observed them in association with parkinsonian states, as well as in the senium, and he

19. Hofmeister, F.: Experimentelles über Gewebsverkalkung, München. med. Wchnschr. **56**:1977-1978, 1909.

20. Dr. Heinrich Waelsch, biochemist of the department of neurology, Columbia University College of Physicians and Surgeons, gave me the opportunity of discussing this subject with him.

21. Alzheimer, A.: Ueber die Abbauvorgänge im Nervensystem, Deutsche Ztschr. f. Nervenh. **50**:5, 1914; Beiträge zur Kenntnis der pathologischen Neuroglia und ihrer Beziehungen zu den Abbauvorgängen im Nervengewebe, in Nissl, F., and Alzheimer, A.: Histologie und Histopathologie. Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1910, vol. 3, pp. 401-562.

22. Stürmer, R.: Die "Corpora amylacea" des Zentralnervensystems, in Nissl, F., and Alzheimer, A.: Histologie und Histopathologie. Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1913, vol. 5, pp. 417-518.

23. Lewy, F. H.: Ueber die Entstehung der Einschlusskörper und ihre Bedeutung für die systematische Einordnung der sogenannten Viruskrankheiten, Deutsche Ztschr. f Nervenh. **124**:93, 1932; Die Lehre vom Tonus und der Bewegung, Berlin, Julius Springer, 1923.

therefore denied a relation between such bodies and infectious disease. I [12] suggested a differentiation of the inclusion bodies into three types: one arising from fat, the second caused by changes in axons and fibrils and the third formed by nuclear excretion. Only the third kind may be characteristic of infectious diseases, whereas inclusion bodies of the first and second types, associated with amaurotic idiocy, may be evidence of degenerative metabolic processes. But the latter two types, though characteristic of noninfectious disease, are also seen with infectious diseases. Thus, Godlowski [24] observed argentophobic inclusion bodies in cases of lethargic encephalitis and in Parkinson's disease, as did Lewy,[23] who, as previously mentioned, noted them in addition with senile and presenile states. The simultaneous presence of amyloid bodies in these conditions is well known (Adolf and Spiegel [25]).

Some scientists identify the inclusion bodies in amaurotic family idiocy with those seen in myoclonic states. First described by Lafora,[26] and later by Lafora and Glück,[27] in cases of myoclonus epilepsy, these inclusion bodies resemble amyloid bodies and give similar staining reactions. Some of these bodies are argentophobic; some show a concentric arrangement and are also noted in glia cells (Davison and Keschner [28]). Though these inclusion bodies are not specific, there is no doubt that they are seen in the great majority of cases of myoclonus, an indication of some relation to these states. In cases of amaurotic family idiocy in which inclusion bodies were present it is difficult to be sure whether such myoclonia existed, for the description of twitchings in these cases is inadequate and can hardly be evaluated. In Bielschowsky's [3] case there was real epilepsy; in addition there occurred daily attacks of convulsions in the trunk and the muscles of the extremities, with fixation of the eyes, seizures which he called petit mal. In Hassin's [8] case the parents told of "marked clonic contractions in the face, eyelids, and extremities," and examination revealed that the eyelids and the muscles of the lower extremities exhibited constant twitchings. In Liebers' [9] case there was real myoclonus epilepsy associated with amaurotic idiocy, whereas in the first case of von Sántha [6] no twitchings were mentioned; in his second case there was tremor, which was relieved by phenobarbital, and in the third case there were convulsions resembling eclampsia and clonic convulsions in the distribution of the left seventh nerve and the upper extremities, occasionally lasting a few minutes. In case 1 in my series there were also myoclonic twitchings associated with epilepsy, resembling those in the case of Liebers.[9]

Thus it seems that in amaurotic family idiocy inclusion bodies are associated with convulsive states or myoclonia. In view of the fact that occasionally there are similar inclusion bodies in cases of Parkinson's disease and of postencephalitic parkinsonian states (Lewy,[23] Godlowski [24]), it is understandable that they should be seen in a case of amaurotic family idiocy with tremor (second case of von Sántha [6]). Rarely, the inclusion bodies are absent in a case of myoclonia, or they are present without the occurrence of myoclonia (first case of von Sántha [6]). Thus,

24. Godlowski, W.: Die Ganglienzelleinschlüsse in der Substantia nigra, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **33**:14-23, 1931.

25. Adolf, M., and Spiegel, E. A.: Zur Pathologie der epidemischen Encephalitis, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **23**:36-66, 1922.

26. Lafora, G. R.: Ueber das Vorkommen amyloider Körperchen im Innern der Ganglienzellen, zugleich ein Beitrag zum Studium der amyloiden Substanz im Nervensystem, Virchows Arch. f. path. Anat. **205**:295-303, 1911.

27. Lafora, G. R., and Glück, B.: Beitrag zur Histopathologie der myoklonischen Epilepsie, Ztschr. f. d. ges. Neurol. u. Psychiat. **6**:1-14, 1911.

28. Davison, C., and Keschner, M.: Myoclonus Epilepsy, Arch. Neurol. & Psychiat. **43**: 524-545 (March) 1940.

one must admit that the inclusion bodies are of essential significance in myoclonic states. But they are not specific. They merely indicate that a particular kind of degeneration or metabolic cell change occurs more frequently with myoclonia than with other states. It may be emphasized that these other states are frequently associated with convulsions or hyperkinesia (epilepsy, Parkinson's disease, and perhaps postencephalitic parkinsonism). The time factor seems to play a role in the formation of the inclusion bodies in amaurotic family idiocy. Thus, in von Sántha's [6b] youngest patient the disease lasted eighteen months; Hassin's [8] patient suffered almost four years, Liebers' [9] patient was ill for three years, and the patient in case 1, two years and nine months, a period almost the same as that for von Sántha's [6b] second patient (two and a half years). It is questionable, however, whether the time factor is the principal one. According to Liebers,[9] two factors are operative in amaurotic family idiocy with myoclonia, one producing amaurotic idiocy and the other myoclonia. On the contrary, there is one common factor in the cases of amaurotic idiocy, namely, fat, which forms the content of the ganglion cells as well as that of the inclusion bodies.

In the papers on myoclonia associated with amaurotic family idiocy it is emphasized that the inclusion bodies are seen throughout the brain—for example, in Hassin's [8] case, in the nucleus ruber and the substantia nigra. As previously mentioned, case 1 resembles the case of Liebers.[9] The part most affected is the cerebellum, where the dentate nucleus is severely damaged and contains inclusion bodies. From his studies on the normal and the pathologic structure of the dentate nucleus in man, Tronconi [29] concluded that the described lesions of this nucleus are not specific, with one exception, namely, the inclusion bodies associated with myoclonus epilepsy.

Since all the parts of the brain which are held to be connected with hyperkinetic states are affected in cases of amaurotic family idiocy with myoclonia, it seems obvious that the site of the process, rather than the inclusion bodies, is responsible for the clonism. This opinion is in agreement with the view of Guillain and Mollaret,[30] who suggested a broader basis for the lesions leading to myoclonia (dentate nucleus–red nucleus–inferior olive). On the other hand, in a case of dyssynergia cerebellaris myoclonica (Ramsay Hunt [31]) the dentate system was affected, as in case 1.

There arises the question how the signs and symptoms in amaurotic family idiocy are produced. These signs are manifold. As a rule, one distinguishes a functioning and a vegetative part in the ganglion cells, a division which was first applied in cases of amaurotic family idiocy by Bielschowsky.[3] Since the functioning part of the cells, the fibrils, remains intact for a long time, the influence of the severe changes in the cell plasma on the signs and symptoms may be comparatively small. In cases of longer-lasting disease the fibrils also are obviously damaged, followed by complete disintegration and disappearance of the ganglion cells. In such cases there are also lesions in the myelin sheaths associated with secondary degenerations and, of course, the corresponding clinical signs.

The clinical signs in the motor sphere are represented by general weakness and hypotonia. This weakness by no means resembles the paresis or paralysis in cases of degeneration of the anterior horn cells, for, according to Sachs,[1a] the

29. Tronconi, V.: Osservazioni sulla fine struttura normale e patologica del nucleo dentato umano, Riv. di pat. nerv. **40**:137-240, 1932.

30. Guillain, G., and Mollaret, P.: Études neurologiques, Paris, Masson & Cie, 1936, series 7, pp. 3-83.

31. Hunt, R.: Dyssynergia Cerebellaris Myoclonica: Primary Atrophy of the Dentate System, Brain **44**:490, 1921.

reflexes are usually present and the electrical reactions of the muscles are normal except for occasional slight diminution of the response to the faradic current. I,[11] therefore, concluded from my recently published case "that every change in the vegetative part of a cell results in a change of the function of the nervous part," but that the asthenia in this case may have been caused in part by involvement of the adrenal system. Since the thymus was also severely damaged, this causative factor must also be taken into consideration. The atonic asthenia in amaurotic idiocy is quite different from the well known flaccid paralysis associated with degeneration of the anterior horn cells, and is therefore, if not entirely independent of the cell changes, dependent on them in part only. The cholinergic and the adrenergic factors are obviously damaged in a similar manner, as in myasthenia or in Addison's disease. In cases 1 and 2 the thymus and the adrenal glands were

Fig. 9 (case 1).—Degeneration of the pyramidal tract. Weigert stain.

altered, but these changes must be studied more accurately before they can be evaluated. It may be remarked parenthetically that Oppenheim's congenital myatonia obviously belongs also to this group of hypotonic asthenias. There are the same weakness and hypotonia, the same electrical reaction and the same position of the arms (handle position) and legs, followed by contractures, as are seen with amaurotic idiocy (Marburg [32]).

In some cases of infantile familial amaurotic family idiocy signs of pyramidal disturbance occur, as in case 1, the result of degeneration of the pyramidal tract (fig. 9).

The most striking sign in amaurotic family idiocy is a negative one, the lack of sensory disturbances. As for the hyperpathia described in all cases of this disease, one must bear in mind that every blind person may be startled by a slight

32. Marburg, O.: Zur Klinik und Pathologie der Myatonia congenita (Oppenheim), Arb. a. d. neurol. Inst. a. d. Wien. Univ. **19**:133-154, 1912.

touch or a sudden noise. In any case, it is surprising that such severe damage of all sensory cells (spinal ganglion; posterior horn) has no other consequence than hyperirritability.

The optic nerve is affected in such a manner as to produce blindness. The white papilla indicates demyelination of the optic nerve, caused by the changes in the retina cells and their disappearance. The disappearance of many ganglion cells and the severe impairment of the outer fiber layers of the cerebral cortex doubtless cause the idiocy, but the characteristic change in the cortical cells does not result in any other signs. As long as fibrils remain intact and there are no secondary degenerations, the vegetative changes in the ganglion cells are obviously not followed by clinical signs seen with lesions involving degeneration of the functioning part.

With respect to these facts there is no difference in the various forms of amaurotic family idiocy. Most authors, however, emphasize differences between Pick-Niemann disease and other forms of the disease, though the former condition resembles infantile amaurotic family idiocy in many respects. These differences concern the kind of fat within the cells, the occurrence of secondary changes in the affected ganglion cells and the site of the process (in amaurotic family idiocy, the nervous system principally and in Pick-Niemann disease, the whole body). Infantile amaurotic family idiocy and Pick-Niemann disease are identical with regard to affinity of the fat for hematoxylin, whereas the constitution of the fat is different (Klenk [33]). The fat in Pick-Niemann disease is sphingomyelin; that in infantile amaurotic family idiocy contains a fatty substance resembling the cerebrosides (Klenk [33]). This fat in the infantile type presents some of the characteristics of phosphatides—hematoxylinophilia, for instance. In cases of the late infantile form this fat is substituted in great degree by sudanophilic or osmophilic granules, commonly regarded as neutral fat, which is otherwise seen only in cases of the juvenile and adult types. Von Sántha [6] noted diminution of hematoxylinophilic granules in his cases; these granules stained light orange with scarlet red. In the present case 1 there was also diminution of hematoxylinophilic granules, and in some cells there were very fine granules of a sudanophilic or osmophilic nature. It seems that in cases of longer duration—the shortest period in von Sántha's cases was eighteen months, and in his third case the duration was two and a half years, almost like that in case 1—there is a final transformation of lipoids into a fat that stains with osmic acid and with scarlet red (neutral fat[?]). Thus, the difference in the lipoids in infantile and in later forms of amaurotic family idiocy may be due merely to the duration of the process.

As for the site of the process, it may be emphasized that the intensity of the damage varies in different regions in different cases. Sometimes the cerebellum and sometimes the striopallidum are severely altered, with production of the corresponding local signs. The cause of this rather individualistic reaction has not yet been revealed. But it certainly is a severe lesion, a lack of functioning tissue, which produces the local signs.

Thus Bielschowsky's [3] suggestion that some peculiarities seen in cases of juvenile amaurotic family idiocy are not present in cases of the infantile type, the degenerations for instance, appears untenable. All changes observed in cases of juvenile amaurotic family idiocy are also seen in those of infantile amaurotic family idiocy if the duration is only long enough.

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33. Klenk, E.: Beiträge zur Chemie der Lipoidosen, Ztschr. f. physiol. Chem. **262**:128, 1939.

SUMMARY

Investigation of several cases of infantile amaurotic family idiocy has revealed the existence of inclusion bodies and severe secondary cell degeneration.

The inclusion bodies are partly argentophilic and partly argentophobic, depending on the kind of fat which forms their basis.

In cases in which inclusion bodies are present there are almost always myoclonic states.

Precipitations outside the cells are caused by degeneration of axons. It cannot be definitely decided whether there are also precipitations from the tissue fluid (Alzheimer and Stürmer).

The clinical signs in cases of infantile amaurotic family idiocy are due only in part to the well known cell changes, which affect merely the vegetative, and not the functioning, portion (fibrils). Only when the functioning part also is affected do neurologic signs appear.

The atonic asthenia, like that in myasthenia or in Addison's disease, is to be explained by a disturbance in cholinergic and adrenergic factors, obviously the result of changes in the thymus and the adrenals which are observed with infantile amaurotic family idiocy.

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FATAL CEREBROVASCULAR ACCIDENT ASSOCIATED WITH CATATONIC SCHIZOPHRENIA

REPORT OF A CASE

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A classic description of acute fatal catatonia was given by Calmeil [1] in 1832. The prominent features observed by him were vivid hallucinations, vasomotor instability and fluctuation from wild hyperactive states to profound stupor. There was rapid progression of the illness to death. He added: "The autopsy explains nothing."

After a lapse of one hundred and ten years this statement still holds good. The neuropathologist has found little in studies of fatal catatonia that can be considered as the specific anatomic substrate of the syndrome. Reichardt,[2] Josephy,[3] Scheidegger,[4] Stauder [5] and Jahn and Greving [6] report the presence of "brain swelling" in some of their cases of sudden death during an episode of acute catatonia, but this is by no means a consistent observation.

From the microscopic standpoint, many detailed accounts of neuropathologic changes have appeared. Goldstein [7] reported changes in the ganglion cells, focal necrobiotic lesions and glial activity in the cerebral cortex. Josephy [3] made essentially the same observations, emphasizing their diffuse character. Vascular stasis and perivascular hemorrhages were noted by Claude and Cuel [8] and also by von Braunmühl.[9] Spielmeyer [10] noted similar lesions but called them nonspecific. He pointed out that he found just such changes in the brains of normal persons, as well as of persons with pathologic conditions not primarily associated with dementia.

The most recent addition to the literature of acute schizophrenic catatonia is the case reported by Malamud and Boyd.[11] Their patient was a 20 year old woman

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1. Calmeil, cited by Ladame, C.: Psychose aiguë idiopathique ou foudroyante, Schweiz. Arch. f. Neurol. u. Psychiat. **5**:3, 1919.

2. Reichardt, M.: Hirnschwellung, Allg. Ztschr. f. Psychiat. **75**:34, 1919.

3. Josephy, H.: Beiträge zur Histopathologie der Dementia praecox, Ztschr. f. d. ges. Neurol. u. Psychiat. **86**:391, 1923.

4. Scheidegger, W.: Katatone Todesfälle in der psychiatrischen Klinik von Zürich von 1900 bis 1928, Ztschr. f. d. ges. Neurol. u. Psychiat. **120**:587, 1929.

5. Stauder, K. H.: Die tödliche Katatonie, Arch. f. Psychiat. **102**:614, 1934.

6. Jahn, D., and Greving, H.: Untersuchungen über die körperlichen Störungen bei katatonen Stuporen und der tödlichen Katatonie, Arch. f. Psychiat. **105**:105, 1936.

7. Goldstein, K.: Zur pathologischen Anatomie der Dementia praecox, im besonderen der plötzlichen Todesfälle bei derselben, Monatschr. f. Psychiat. u. Neurol. **25**:565, 1909.

8. Claude, H., and Cuel, J.: Notes anatomo-cliniques sur trois cas de délire aigu, Encéphale **22**:628, 1927.

9. von Braunmühl, A. V.: Ueber Gehirnbefunde bei schweren Erregungszuständen, Ztschr. f. d. ges. Neurol. u. Psychiat. **117**:163, 1928.

10. Spielmeyer, W.: Kreislaufstörungen und Psychosen, Ztschr. f. d. ges. Neurol. u. Psychiat. **123**:536, 1930.

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who showed hypotension, acrocyanosis and menstrual irregularities during nine months of hospitalization. During a period of catatonic excitement she lapsed into coma. There followed a series of generalized convulsions, signs of meningeal irritation and hyperpyrexia. Death occurred sixty-eight and a half hours after the onset of the acute episode. Anatomic studies revealed multiple, discrete and coalescing areas of hemorrhagic encephalomalacia throughout the cortex of the cerebrum and the cerebellum. Many of these areas were rather large. There were no evidences of a major vascular accident; in fact, no changes were demonstrated in the blood vessels. The authors attributed the lesions to a functional disturbance of the cerebral circulation associated with constitutional vasomotor lability, and not directly to the psychosis.

REPORT OF CASE

History.—S. L. J., a 22 year old white man, was admitted to St. Elizabeths Hospital on May 2, 1942.

One brother was said to have suffered from a "nervous breakdown." The patient ran away from home because of discontent with the family situation. Shortly afterward he enlisted as a yeoman in the United States Coast Guard. He had two years and seven months of active duty, with a good conduct rating, before the present illness.

On April 29, 1942 the patient wedged himself in the bilges of a coast guard cutter; the reason he gave for this act was: "I'm a coward." He was admitted to the United States Marine Hospital, Norfolk, Va., on the following day. While there he was disturbed and negativistic, appeared to be deeply concerned about loyalty to his mother and to his country, manifested delusions of unworthiness and declared that he believed he had syphilis. Insight was lacking, and judgment was faulty. Asked to undress, he at first refused to do so, but later tore off his clothing. He escaped from a locked room by destroying a heavy screen, ran down a fire escape in the nude and attempted to start a truck and leave the hospital grounds. It was necessary to employ several orderlies to subdue him. He was then transferred to the United States Naval Hospital, Bethesda, Md., and from there to St. Elizabeths Hospital.

He arrived on a stretcher, in restraint. He was mute except when in a cold pack. At such times he talked freely, but often incoherently. His emotional reactions were inappropriate. Lability of mood was striking. He admitted having auditory hallucinations and expressed many delusions. Attention wandered, and comprehension was faulty. He was disoriented for place.

Physical Examination.—Examination disclosed a well built young man with dusky red-mottled skin. The blood pressure was 128 systolic and 96 diastolic and the pulse rate 90 beats per minute. The pupils were round and equal. They reacted briskly to light and in accommodation. The optic disks were flat. No retinal vascular abnormalities were observed. The deep reflexes were equal and active on the two sides. The only abdominal reflex obtained was in the right lower quadrant. The whole body surface was practically immune to superficial pain. Perception of pressure pain was diminished.

The diagnostic impression was dementia praecox (schizophrenia), catatonic type, with affective features.

Course of Illness.—He was violent and profane and needed restraint except when under the influence of sedative drugs. Cold packs were also useful in calming him. He refused to eat; it was necessary, therefore, to resort to tube feeding on the third day in the hospital. This could be accomplished only after the intravenous administration of sodium amytal (3¾ grains [0.24 Gm.]). After the feeding he manifested no weakness of the arms or legs. He displayed many infantile mannerisms.

Sometimes during the night he lost the use of the right arm and leg. He was found lying on the floor, unable to move these extremities. Neurologic examination now revealed weakness of the right side of the face; right flaccid hemiplegia; absence of deep reflexes in the right arm; absence of abdominal reflexes on the same side, and a positive Mayer's sign. The blood pressure was 130 systolic and 80 diastolic, the pulse rate 92 and the temperature 100 F. (rectal). Lumbar puncture made shortly afterward demonstrated an initial spinal fluid pressure of 140 mm. of water. The specimen was clear and colorless. There were 4 cells per cubic millimeter; the protein content was not increased. The Kolmer and colloidal gold reactions were negative.

Eight hours later the patient was in deep stupor. The blood pressure had fallen to 75 systolic and 52 diastolic. The temperature remained elevated. The neck was not stiff. Breathing was slow and deep, and there was a noticeable lag of the right side of the thorax. During periods when he partially awakened he appeared to be completely aphasic. Confrontation examination of the visual fields at these times demonstrated probable right homonymous hemianopia. Occasionally there was skew deviation of the eyes. The pupils were round, equal and moderately dilated. The optic disks were not edematous. No vascular or retinal changes were noted. Sucking and biting reflexes were elicited with ease. There was weakness of the right side of the face of supranuclear type. The right arm and leg were flaccid and immobile. A grasp reflex was present in the right hand. The deep reflexes were active and equal in the two arms but were accentuated in the right leg. Cutaneous reflexes could not be obtained. The Hoffmann response was demonstrable in

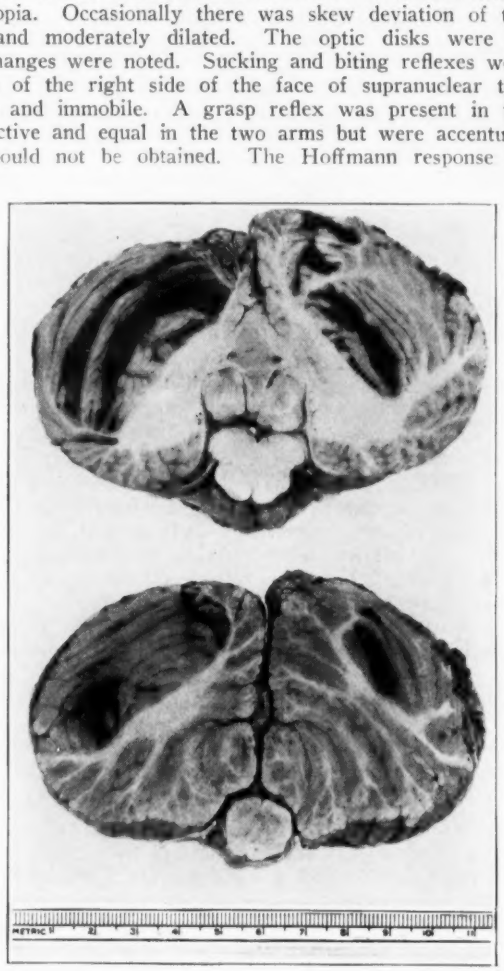

Fig. 1.—Subarachnoid and parenchymal hemorrhages in the cerebellum.

both hands, but the plantar reaction was flexor in type. Sustained ankle clonus was elicited bilaterally. Appreciation of pinprick was reduced over the whole right half of the body.

The patient was given 500 cc. of blood plasma and, later, 1,000 cc. of 10 per cent dextrose in saline solution. One hundred milligrams of nikethamide, 50 mg. of thiamine hydrochloride and 100 mg. of ascorbic acid were administered intravenously. By this time his general condition was somewhat improved, and the blood pressure had risen to 120 systolic and 70 diastolic. Aspiration of much mucopurulent material from the tracheobronchial tree resulted in the disappearance of coarse rales from the lower lobes of the lungs.

He lived five days longer, his condition fluctuating between stupor and wakefulness. During the intervals of wakefulness he became active and combative and had to be restrained. The neurologic status remained essentially unchanged. Many examinations of the eyegrounds failed to disclose choking of the disks. A blood count revealed moderate leukocytosis but no increase in the number of erythrocytes. The bleeding and clotting times were normal. A second spinal tap, on the sixth day in the hospital, yielded no fluid. Repeated aspiration of the chest and sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) medication resulted

in a temporary fall of body temperature to a nearly normal level. On the ninth hospital day the temperature again rose, however, to 104 F. (rectal); the respirations became slow and labored; generalized cyanosis appeared, and the patient died.

Necropsy.—Postmortem examination was performed eighteen hours after death by Dr. K. H. Langenstrass. The body was that of a well developed and well nourished young man. There were a number of small abrasions in the gluteal region. The subcutaneous fat and the pectoral and abdominal muscles were rather dry. The heart was dilated, poorly contracted and soft. There were no valvular or myocardial lesions. The aorta and the large vessels were thin walled and elastic. The aorta measured only 40 mm. in diameter at the level of the celiac axis. The lungs showed marked hypostatic congestion and edema. There was purulent bronchitis. The abdominal viscera showed no evidence of a disease process, except for pronounced hyperemia. The endocrine system appeared grossly normal.

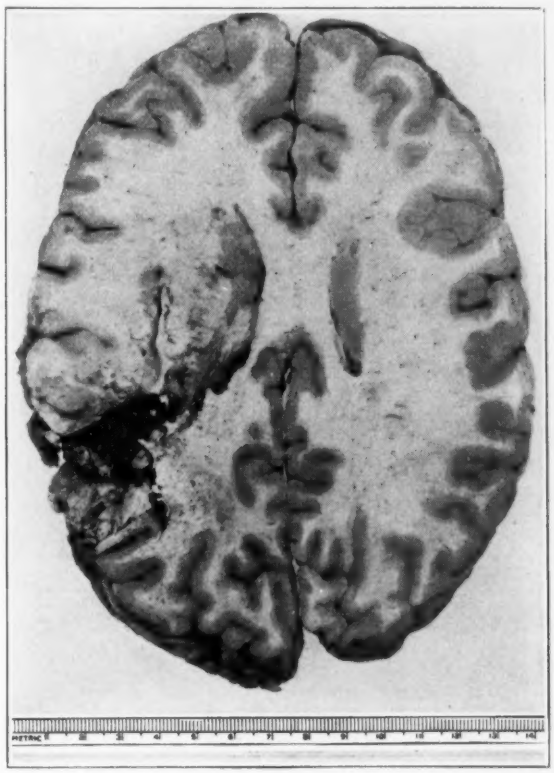

Fig. 2.—Hemorrhage in the left parietal lobe and extensive softening in adjacent tissue.

Brain: The brain was large and weighed 1,520 Gm. The dura and leptomeninges were somewhat dry and congested. There were several small subarachnoid hemorrhages. The cerebral convolutions were flattened and broad. The left hemisphere was more voluminous than the right. There was a fairly extensive, but poorly defined, softening in the left parietotemporal region; it included areas 40, 41 and 42 of Brodmann. The vessels forming the circle of Willis and its branches were thin walled and of average caliber. The internal carotid and middle cerebral arteries were dissected. The posterior branch of the left middle cerebral artery was filled with a soft red thrombus, which completely occluded the vessel. The anterior branch and the corresponding vessels on the right were empty. There were extensive, more or less symmetric subarachnoid hemorrhages in the cerebellum (fig. 1). The extravasations of blood extended slightly into the parenchyma. The source of the hemorrhage could not be determined.

Dissection of the cerebral hemispheres disclosed a large, firm blood clot in the left parietal region (fig. 2). The hemorrhage was well circumscribed. The tissues adjacent

to the clot were extremely friable. Almost the entire middle third of the left hemisphere showed areas of ischemic and hemorrhagic necrosis (fig. 3). The left frontal pole and the left occipital lobe were uninvolved. The left lenticular nucleus was dotted with numerous small hemorrhages. The adjacent anterior limb of the internal capsule was somewhat soft. The posterior limb, the caudate nucleus and the thalamus appeared intact. The cortex and subcortex of the left parietal lobe were very soft. A circumscribed hemorrhage lay close to the wall of the posterior horn of the lateral ventricle. The ependyma was intact. The area of infarction was smaller in ventral levels. Relatively large portions of the basal ganglia showed no gross changes at these levels. The infarct extended into the left temporal lobe, but the temporal pole was intact. The occluded vessel may be identified in the sylvian fissure in figure 4. All other vessels were narrow, thin walled and empty. The right hemisphere was free from gross lesions.

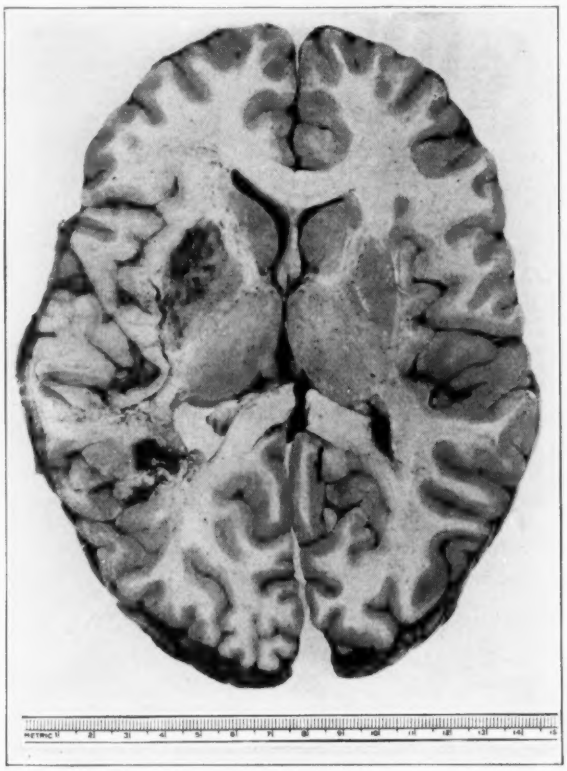

Fig. 3.—Areas of hemorrhagic and ischemic necrosis in the left cerebral hemisphere.

Microscopic Examination.—Brain: Histopathologic studies were made of sections from the left frontal, paracentral, parietal and occipital regions; the right frontal, paracentral, parietal and temporal areas; the neocerebellum, the mesencephalon, the medulla oblongata and the occluded branch of the left middle cerebral artery. The following staining technics were employed: hematoxylin and eosin, thionine, phosphotungstic acid hematoxylin and the Weil, Davenport, Heidenhain and Perdrau stains.

The leptomeninges were everywhere thin but showed areas of decided focal fibrosis, especially over the right and left paracentral lobules. There were marked hypervascularity and congestion. Small subarachnoid hemorrhages were present in all sections except those of the medulla oblongata. The hemorrhages were evidently recent, as the erythrocytes were well preserved and there was little hemosiderin pigmentation.

The occluded branch of the left middle cerebral artery had an exceedingly thin wall, apparently free from disease. It was filled with a thrombus, which had partially contracted away from the vessel wall, carrying the endothelium with it. A small series of interrupted

serial sections was made of the occluded vessel. In some areas red blood cells lay between the detached thrombus and the injured wall of the vessel. The erythrocytes composing the thrombus were for the most part well preserved. There was only slight hemosiderin pigmentation. The red cells were closely packed, and there was relatively little formation of fibrin. White blood cells were not numerous. There was a certain amount of lamination at the periphery of the clot. In one area there was a small group of fibroblasts. Nearby were a few narrow empty channels lined with endothelium.

Parenchymal vessels were greatly engorged. The capillaries in the gray matter were hyperplastic. Many small hemorrhages were observed in every section except those of the medulla oblongata. In the left parietal lobe, where larger extravasations of blood appeared, the ruptured walls of vessels were demonstrable. Ruptured vessels were also noted in the right parietal lobe. A few small vascular channels in various areas were filled

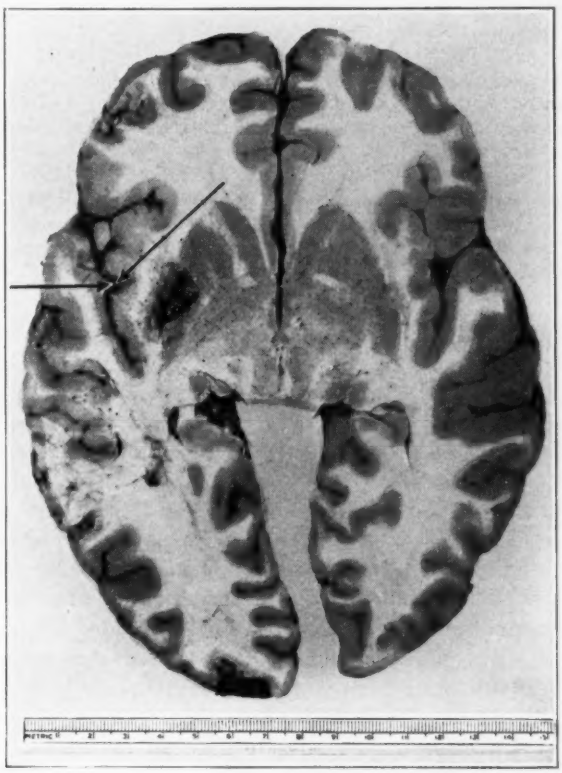

Fig. 4.—Hemorrhagic infarct in the left lenticular nucleus and infarction of the left temporal lobe. Arrows point to the occluded left middle cerebral artery.

with hyaline thrombi. Occasional arterioles showed proliferation of their lining cells. A number of capillaries, and larger vessels too, were lined with swollen endothelium. There were rare slight perivascular accumulations of granulocytes, round cells and pigmented reticuloendothelial cells.

A section from the left parietal lobe included a portion of the hemorrhagic infarct. Scattered throughout the section were irregular areas of tissue rarefaction, where myelin sheaths and nuclear elements were reduced in number. A few of these pale, spongy areas lay in the vicinity of engorged blood vessels. There was conspicuous loss of nerve cells in the areas of cortex near the superficial hemorrhages. The remaining neurocytes were severely damaged. They were usually pale and shrunken or were undergoing lysis. There was no proliferation of the glia or mobilization of polymorphonuclear leukocytes. Gitter cells were not seen. A few macroglia cells had hypertrophied, folded nuclei. They thus resembled Alzheimer glia cells. Some gliacytes were disintegrating. Edema was evidenced by many "pericellular spaces" and dilated Virchow-Robin spaces.

In other areas lamination and polarity of nerve cells were only fairly well preserved. There were numerous scattered empty spaces. The majority of neurocytes showed ischemic, homogeneous changes. Apical dendrites were notably thickened in many instances. Some of the ganglion cells had pale, more abundant cytoplasm, but even these rarely contained any Nissl substance. Cytolysis was sometimes observed. There were a few shadow cells.

Proliferation of gliacytes was slight except in the mesencephalon. In the tectum of the midbrain, the microglia and macroglia cells were hypertrophied, and three mitotic figures were observed. A minute focus of gliacytes and small round cells was noted in one peduncle.

In the left frontal lobe there was scattered marginal fibrillary gliosis, and one large warty nodule of glia fibrils projected into a sulcus. Unusually large ependymal granulations were observed in the posterior horn of the left lateral ventricle. In the aqueduct a single exceptionally large glial nodule projected into the cavity from the floor. It was attached by a narrow band of ependymal cells, so that it resembled a small tumor rather than a granulation. A few small, shallow granulations were noted in the lining of the inferior horn of the right lateral ventricle.

Myelin sheaths were intact except in the parietal lobe, where the number was reduced in the rarefied spongy areas. The sheaths that remained in these areas were widely separated and occasionally showed slight focal swellings. Some of the destruction of myelin occurred at the junction of the gray and the white matter, so that there was focal destruction of U fibers in such regions.

Other Organs: Sections from the abdominal and thoracic viscera showed widespread focal congestion and stasis. In the lung were a number of small hemorrhages and early bronchopneumonia. There was slight infiltration with lymphocytes and plasma cells in the interlobular connective tissue of the liver. In none of the sections was there any evidence of disease of the vessel walls.

COMMENT

The sudden onset of a cerebral accident in a young, well preserved person with no objective evidence of generalized vascular disease is rare. The history of previous good health, equivocal neurologic signs at the time of admission, absence of injury to the head and almost acellular spinal fluid make the probability of occlusion of the left middle cerebral artery with cerebral infarction the most reasonable diagnosis.

This case, and the one reported by Malamud and Boyd, are apparently unique in that such extensive, grossly demonstrable damage occurred in the brain. In general, in most of the cases of fatal acute catatonic excitement reported in the literature only microscopic changes, or none at all, were present.

In our case the small areas of loss of nerve cells, minor pathologic alterations in the neurocytes and slight glial reaction, while similar to changes reported in other cases of acute schizophrenia, are not considered significant.

The vessel walls did not appear diseased. The scattered vascular "blow-outs" in both cerebral hemispheres may well have been an expression of cerebral vasomotor hyperactivity. If true, this might substantiate the theory of von Braunmühl [9] and Spielmeyer [10] that functional circulatory disturbances operate as an important factor in acute catatonic excitement. The factors responsible for the thrombosis of the posterior branch of the left middle cerebral artery in our case were not demonstrable.

The clinical features of our case, together with the fatal termination, correspond closely to those in many other recorded cases of "schizophrenic death."

SUMMARY

A 22 year old man with schizophrenia died twelve days after the onset of an acute catatonic episode and five days after the sudden development of right hemiplegia. Negativistic and assaultive behavior, lability of mood, colorful and bizarre hallucinatory and delusional mental content, expression of guilt feelings, confusion and disorientation were outstanding features of the psychosis. Manifestations of vasomotor lability comprised the striking physical observations prior to the development of

the neurologic signs. At autopsy thrombosis of the left middle cerebral artery was observed. There were hemorrhage and infarction in the left parietotemporal region and extravasations of blood in the subarachnoid spaces and the parenchyma of the cerebellum. The underlying cause of such extensive anatomic damage was not ascertained. The clinical resemblance of this case to other reported instances of "brain death" associated with catatonic schizophrenia is noted. The explanation of the lethal vascular accident is thought to lie in functional circulatory changes often associated with this form of mental illness.

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St. Elizabeths Hospital.

DR. H. DOUGLAS SINGER'S CONCEPT OF THE PSYCHOSES

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Dr. H. Douglas Singer was one of the leading psychiatrists in this country, so that it now seems fitting to present some of the psychiatric concepts he had formulated during the later period of his life. We, who were members of his staff for many years, have attempted in this paper to give a brief outline of the development of his ideas concerning the psychoses. All of the views herein presented are in essence those of Dr. Singer. So far as possible, his own words have been retained.

Since the opening of the Psychiatric Institute of the University of Illinois College of Medicine, in 1931, it has been customary to present a case history of a patient at the weekly staff meeting. After the reading of the history by a member of the staff, there followed a general discussion of the problems involved. Dr. Singer was practically always present at these meetings, and his interpretations of the facts at hand, as well as his general comments on matters of psychiatry, were always particularly stimulating to the group. His keen criticism, his stress on logical thinking and his wisdom in demanding that basic pathologic processes be sharply separated from precipitating environmental factors were outstanding in his approach to an understanding of mental illness.

Even before the advent of shock therapy and the growing realization of the role of the integrative machinery of the body, particularly the autonomic nervous system, in the psychoses, he began to formulate his theory of the psychosis as a disturbance of this machinery. As will be seen later, he finally adopted the point of view that manic-depressive psychosis and schizophrenia have a similar location pathologically in the autonomic integrating centers.

At the Psychiatric Institute there are available stenographic notes of the discussions on some 400 case histories which were presented at staff meetings, with final diagnoses made by Dr. Singer. In the belief that his statements are of inestimable value for an understanding of mental disease, an attempt is here made to trace the development of his theories of the psychoses during the period that he was director of the institute, from 1931 until his death, in 1940, and to summarize briefly his point of view regarding the various psychoses.

SCHIZOPHRENIA

In the early staff discussions, patients with schizophrenia simplex were found to show characteristically a progressive loss of interest and affect over a number of years, but not necessarily acute psychotic disturbances or evidence of splitting. Interest was considered a response of the organism as a whole and a matter of affectivity as this arises from drive or energy which is vegetative in origin. Interest thus was regarded as a matter of body organization. Although the loss in schizo-

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phrenia simplex does not concern intelligence, with diminution of emotional drive, which makes the expression of intelligence feasible, intelligence is not used to advantage.

The cause of schizophrenia simplex was at first regarded as an active disease process which is progressive and destructive, the loss becoming more evident as greater demands are made on the organism, until finally there is reduction to a low level of response, manifested by such activities as appetite and masturbation. Thus a deterioration occurs, a progressive chronic dementia, which may also characterize hebephrenic schizophrenia in some instances, although the latter has other features which distinguish it from schizophrenia simplex, features which comprise the descriptive term hebephrenic and may include an ultimate condition of stasis.

During this period (1933) the classification of hebephrenia was sometimes applied (1) to cases in which there was a constitutional defect in the form of passivity and a fundamental lack of drive from early life, (2) to cases in which it seemed justifiable to infer that a progressive disease process was present, producing a loss of mental function and (3) to cases in which there was neither a lack of fundamental drive nor a disease process, but a poor reaction to a situation. This varied usage of the term hebephrenic illustrates clearly the point of view that the form of the psychosis tells nothing of the underlying etiologic factors.

In 1934 it was indicated that in many cases of dementia simplex a structural defect in energy is evident from the start; this defect is the main feature of simple schizophrenia and shows itself in lack of adaptation when the person is no longer protected and has to face definite responsibilities. It is then that his inefficiencies become more evident. This behavior of a person who is poorly constructed to face his difficulties is not due to a disease but is a reaction between his constitution and the environment. He is a biologically inefficient person, and although he may not change, the demands on him may do so. At this time, however, the belief was expressed that, in addition, there is a progressive degenerative change which manifests itself in greater isolation and a let-down in the ability to deal with the reality situations of adult life, due to loss of energy or drive. The latter condition is dementia praecox in the true sense of the word, for it is a dementing process that results in destruction, a progressive loss and not merely an original constitutional deficiency. Thus dementia simplex has an organic substratum and few psychogenic features.

In the paranoid form of schizophrenia, too, the main feature was considered a constitutional defect in the quality of energy, which is the basis of the patient's difficulties in meeting his conflicts and which results in the use of the typical mechanisms of rationalization and projection. As early as 1932 the form of this psychosis, as of all psychoses, was thought to evolve from the type of personality. Thus the paranoid condition is a defect plus a superstructure of psychogenic factors which are expressed as a disturbance of personality. It may be said that the paranoid person is oversocialized. He shows an intense subordination to convention. Such a patient is able to utilize the mechanism of projection because he is endowed with good energy quantitatively, although not qualitatively. This permits of aggression and the blaming of others, rather than the adoption of a passive attitude of self blame for his inefficiencies.

In practically every case of the catatonic form of schizophrenia the presence of a disease process was suggested. The patient does not show voluntary withdrawal from the world but is overwhelmed by an illness which affects the vegetative mechanisms. Although the behavior is catatonic from the descriptive standpoint, this term is in no sense explanatory of the process which gives rise to it, one

which may produce reversible or irreversible and permanent changes. When the process is reversible, the machinery of the higher levels is shut off but not damaged permanently. Thus it is possible to have schizophrenia without dementia.

The catatonic excitement is accompanied by withdrawal from and lack of interest in the outside world; the behavior is not related to the surroundings. This is in contrast to manic excitement, in which the patient manifests an overinterest in the outside world; the pattern of his behavior is controlled by the surroundings; his mood is happy, and he shows an interest in sensory perceptions. The catatonic person, on the other hand, is not happy and shows no interest in his surroundings.

Dr. Singer rejected the idea that schizophrenia is a regression to a more infantile type of behavior, due to a shutting-off of the machinery for reacting at higher levels. He expressed the belief that there is overdevelopment in the other direction, an oversocialization, expressed by the development of too many taboos. Unable to express things in the way he wishes, the patient carries out his wishes in a more primitive manner (1934).

Schizophrenia means splitting at a high level of response. The split is shown, for example, by hallucinations, in which voices are described as coming from without, and by features that are odd and do not seem to be fitting or understandable to the observer, and perhaps to the patient, and that require interpretation or explanation at a psychic level. The verbal expressions are not consistent with the emotional responses or the muscular activity, and this inconsistency is further evidence of a split. Many of the responses are due to internal stimulation, and because they are symbolic they seem odd and inexplicable.

In many cases of schizophrenia there is no history which suggests a defect in constitution. The history may indicate that a change of personality took place abruptly. This was interpreted to mean that an illness had occurred, damage had resulted and, as a result, activity, accomplishment and function were reduced to a lower level. At this time (1934) Dr. Singer stated that he had no conception of the location of the disease process. The condition, however, was regarded as an organic dementia belonging to the group of dementia praecox, for it represents an actual disease process and a progressive loss of mental efficiency.

The term schizophrenia does not signify an entity and is not necessarily descriptive of a disease, but denotes a form of behavior of a psychogenic nature. A situational reaction, for example, is not a disease but may be schizophrenic in the type of behavior shown, the reaction being the patient's way of meeting the threatening situation. Thus schizophrenia is a formal descriptive term for behavior that may occur as the result of a disease process or of a maladjustment to the environment, with personality difficulty. From the beginning of 1934, therefore, the case in which the history suggests that a disease process has occurred at some time during the patient's life has been classified as one of "schizophrenia, organic type." The term schizophrenia is preferable to that of dementia praecox because the condition is not a dementia in the sense of intellectual loss and does not necessarily occur at an early age. In those instances in which the illness was obviously a reaction to the environment, the condition was classified as "schizophrenia, psychogenic type."

Late in 1935 Dr. Singer referred to a given case of schizophrenia as a vegetative disturbance in the same sense that the manic-depressive psychosis is a vegetative disorder. This was the precursor of his theory, later to be advanced,[1] that both

1. Singer, H. D.: Psychosis and the Central Autonomic Nervous System, J. A. M. A. **110**:2048-2053 (June 18) 1938.

the organic schizophrenic psychosis and the manic-depressive psychosis are pathologically the same, namely, disorders of the autonomic nervous system, and that they differ symptomatically because of the type of person who is ill.

It was contended that schizophrenia, psychogenic type, is a disturbance in behavior, schizophrenic in nature, not due to bodily illness. The symptom picture of schizophrenia may be psychogenic if it is a reaction motivated from a higher level (1936). It was stated, however, that the psychoneurosis is due to a relative constitutional weakness, probably a defect in the energy available for reaction, which makes the person less capable of adjusting to external conditions. Although the essential feature of a psychoneurosis is a maladjustment between the person and his environment, and therefore is primarily situational and a personality problem, the failure in adaptation may be extreme enough to necessitate the patient's removal from the environment, so that by definition it may be classified as insanity, which means a condition producing incapacity to manage one's affairs acceptably to society.

When the illness is organic, at a lower level, the manifestations must be studied with the purpose of finding what relation they have to the actual behavior. A person who is reacting at a higher level has insight. Even a psychotic person with schizophrenic hallucinations and ideas of reference knows that these are not real and has insight to that extent. The monotony of ideas in schizophrenia is due to the fact that they do not arise from higher levels of consciousness. The patient does the unexpected; for example, he strikes another patient for no reason. There is no clue to this behavior. The act does not occur because of anything the other person did; it comes from within and is not related to the world outside. Thus schizophrenic behavior is characteristically unpredictable. The pattern is monotonous and repetitious because the motive forces, which come from within, are relatively unchanging, as compared with the rapidly changing stimuli from the outside (1936).

In cases of the organic type the loss is of the emotional reactions, such as initiative, interest and drive. Emotion is a manifestation of energy in the body, and the term dementia was used to mean merely a loss of this energy, although it was recognized that the term dilapidation was preferable. The same sort of loss may occur in the presenile psychoses and in dementia paralytica, in which there is in addition an intellectual loss.

In 1937 psychosis was defined as a disturbance of the autonomic nervous system, which produces a change in the autonomic regulation of activity. Inflammatory and other conditions affecting the central integrating mechanisms may also cause damage to the autonomic machinery, which will account for the emotional changes sometimes associated with dementia paralytica and other diseases primarily of the central nervous system.

Deterioration is due to a disease process in the central autonomic centers, an actual structural change which is irreversible. An active disturbance in these centers will also account for swings of excitation when they occur. These swings may be either manic or schizophrenic in form, depending on the personality.

It was emphasized that the term schizophrenia merely denotes an exaggeration of a personal mode of reaction brought about by stress, which may occur as damage to the integrating mechanisms or may be the result of overwhelming difficulties in the situation. The former constitutes a psychosis; the latter, a psychoneurosis.

After the sorting out of cases of organic schizophrenia, the primary defect at the vegetative level (poor energy but no deterioration) in cases of simple schizo-

phrenia was stressed more and more, and finally the label "simple schizophrenia" was limited to a condition with an obvious defect in constitution. Late in 1938 Dr. Singer stated that it seemed to him worth while to keep the term simple to refer to a constitutional defect which shows itself all through life and to restrict the other names, like hebephrenic, catatonic and paranoid, to refer to those conditions that are not inherited but are due to something that has happened since birth. This concept that simple schizophrenia is a primary defect at the vegetative level (energy), with nothing added, was a departure from the earlier point of view that it is a deterioration due to a disease process. It was recognized, however, that a constitutionally defective person may have superimposed on his defect added stress in the form of actual damage within the organism. Schizophrenia of this type was now classified as organic, the subgrouping depending on the characteristic features of the behavior.

In summary, the schizophrenias may be classified in three types: (1) a defect, which includes simple schizophrenia and some paranoid schizophrenias; (2) an organic disease process, in which the symptom picture may be that of the hebephrenic, catatonic or paranoid form, depending on the person who is ill, and (3) a psychogenic disorder in which, again, the form of the illness may be any of the aforementioned three types. These conditions are properly classified as psychoneuroses.

MANIC–DEPRESSIVE PSYCHOSIS

In 1934 the view was expressed that a manic or depressive reaction is a vegetative upset which influences the higher levels secondarily. The depression, for example, is not a withdrawal but a change in the actual vegetative activity of the body itself. There is a forcefulness about the mood which leads the patient to adopt definite ideas and reactions. In the manic condition, moreover, the expressions are frank and appropriate, and the patient is conscious of their meaning, in contrast to schizophrenia, in which the expressions are unintelligible to the observer, and probably also to the patient, because they are expressions of something unconscious. In a depression the mood may lead the patient to justify it by the use of ideas of self condemnation. The patient utilizes every possibility to express his feelings; this is a secondary reaction through the conscious levels. When chances for adjustment are diminished, doubts and fears apart from the illness will be strongly in evidence. Any one in such a depressed mood will be preoccupied with his own ideas of what is unpleasant and depressing. Such thoughts, however, do not cause the depression.

It was stressed at this time that the term manic-depressive psychosis, like the term schizophrenia, describes not a disease, but a reaction or mode of behavior, the basis of which may be a number of things. The disorder may, for example, be precipitated by an acute infectious illness which disturbs the constitution, or it may arise as the result of a toxic process.

Shortly thereafter Dr. Singer's concept of the manic-depressive reaction was broadened: It was now considered that the condition is a reflection of the personality, and thus may be associated with and characterize any type of illness. A patient with cerebral arteriosclerosis, for example, may manifest typical manic features in his psychosis, or one with dementia paralytica may be depressed. Yet the terms "manic" or "depressed" tell nothing of the underlying illness.

Thus a diagnosis has not been made when a psychosis is labeled "manic-depressive." Some disease may be present which produces a change in the general metabolic activity of the body, or there may be merely an oscillation of mood

beyond the normal limit. The manic-depressive syndrome, however, is not always vegetative in character, since it is merely a product of the personality. But a vegetative illness is not a personality disorder, although one may observe psychogenic features therein, such as phobias, which are personality disorders, that is, variations at a higher level depending on something in the experience of the person. Psychogenic depression does not show the same retardation as the manic-depressive depression, and there is an element of anxiety, which is due to conflict. In most situations of depression in which there is severe agitation one finds a rigid personality. Thus the attitudes of the patient during the depression give it a typical coloring. The same element of personality is involved both in the disturbances of mood which are psychogenically determined and in those which are the result of deranged bodily activity. One must know, therefore, how the depression came about, what it means in the functioning of the body and what is the nature of the disturbance. A true manic-depressive depression involves all functions.

In 1937 Dr. Singer stated that the swings of mood brought about by environmental factors should be classed as psychoneuroses. In these instances the person is reacting to some conflict with the environment—to demands of the environment which arouse emotion. The stress in these instances is psychogenic, and the psychogenic factors in experience determine the form in which the disturbance of mood is expressed. Nevertheless, environmental factors also play an enormous part in precipitating vegetative disturbances in persons who are liable to them, and disturbances thus psychogenically initiated may occur in the psychoses. Sometimes the vegetative imbalance is so great that anything will precipitate a disturbance. There is a tendency to emotional upset which must be regarded as part of the build of the person, in addition to other bodily factors which may precipitate mood swings.

To question whether one is dealing with a manic-depressive disease or with a reactive excitement or depression is only another way of asking the level of the disturbance. Swings in mood may occur only during periods of bodily stress, a stress not related to the environment, which lowers bodily resistance and initiates an upset. A manic-depressive depression is a disturbance on the vegetative level. Often it is extremely difficult to differentiate a psychoneurosis from a vegetative disturbance, for there may be pathologic mood swings in persons who also are neurotic. One striking feature is the monotony in the vegetative disturbance. Most reactive or psychoneurotic persons can be distracted and the agitation of the depression will subside, but this cannot be accomplished with a person who has a more fundamental disorder.

In 1934 the psychosis had been defined as a state of mind that is pathologic in the sense that it is excessive or too prolonged or involves a distortion of reality.

The following year Dr. Singer again indicated that a disturbance, even when precipitated from the outside, may be psychotic in the sense that it is pathologic in degree and duration. He again stressed, however, that all psychotic conditions are reactions, not diseases; they are behavior characteristics of the person who is ill. Whether a condition is manic or schizophrenic, for example, is merely a psychologic or personality classification.

Late in 1937, after the advent of shock therapy and the recognition of the possible role of the autonomic nervous system in mental disorders, the manic-depressive psychosis, like all psychoses, was defined as a disturbance of the central autonomic integrating mechanisms, perhaps pathologically the same as schizophrenia, and differing from it only in form because of differences in the person who

is ill. Whether the patient behaves as a schizophrenic or as a manic-depressive person makes no difference if the disorder occurs at a given biologic level as the result of the same type of bodily chemical change.

Although psychosis was now defined as a disturbance of the autonomic nervous system, the idea was still retained that the main determining factor in the form of the psychosis is the person who is ill, and that the terms "manic-depressive" and "schizophrenic" are merely descriptive of the expressed behavior, not diagnoses of the underlying disease process. Nevertheless, manic-depressive psychosis was now regarded as an organic illness, of central origin, involving the whole organism. The diagnosis is not merely a matter of the recognition of a specific type of persistent oscillation of severe degree in the autonomic adjustments. Instead of showing the normal mood swings, such persons exhibit a tendency toward greater degrees of oscillations, which last for a long time. These swings occur in persons who have such a constitutional makeup, for when the autonomic regulation is inferior in quality, there are more pronounced effects than when the organization is more adequate. Persons who cannot handle ordinary trauma show excessive reactions—to infections or to psychologic stress—which may cause a disturbance of equilibrium beyond the normal range. Such swings occur in both manic-depressive and schizophrenic conditions.

After attacks of what most people call manic-depressive psychosis, there may be deterioration (loss of energy), although this is not common. Such deterioration is due to irreversible damage in the mechanisms of integration, and is obviously organic. It is probably identical with the illness which sometimes appears as a schizophrenic reaction. Disturbances in autonomic integration must result in disturbances of mood. When the expression of mood is frank and extrovert, the condition is classified as manic-depressive psychosis, and when it is introvert and symbolized, as schizophrenia. The typical manic-depressive psychosis may more adequately be labeled a periodic autonomic imbalance, a designation which defines the illness in terms of the underlying pathologic process. Likewise, it was anticipated that the pathologic basis of schizophrenia would some day be described, and that schizophrenia, too, could then be given a name which would connote the basic underlying condition.

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PATHWAYS FOR PAIN FROM THE STOMACH OF THE DOG

OSCAR J. BALCHUM, M.Sc.
AND
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DETROIT

For purposes of description the sensation of pain may be subdivided into two main categories: viz., somatic pain, produced by the noxious stimulation of the peripheral somatic nerves, and visceral pain, experienced after the appropriate stimulation of a viscus. In addition to these more common categories, a third variety of painful sensation, commonly designated as referred pain, is characterized by the fact that the painful sensation is interpreted by the subject as originating from the surface of the body, although it is known to be the result of the noxious stimulation of a viscus far removed from the painful area.

It is generally agreed that stimulation of the parietal pleuroperitoneum by scratching or rubbing results in sensations of pain (Lennander [1]; Alvarez [2]; Morley [3]), whereas stimulation of the visceral pleuroperitoneum is painless (Lennander [1]; Capps and Coleman [4]; Alvarez [2]). Most authors have expressed the belief that the gastric mucosa is insensitive to painful stimuli (Carlson and Braafladt [5]; Alvarez [2]). On the other hand, Boyden and Rigler [6] reported that they produced pain by stimulating the gastric mucosa of human beings with a faradic current. Although deeply seated, the pain was "projected" to the skin, and these painful areas tended to shift with changes in position of the electrodes within the stomach.

It is believed that traction on the mesenteries is a stimulus adequate for the production of pain (Neumann [7]; Breslauer [8]; Adams [9]; Lebendenko and Brjussowa [10]; Alvarez [2]). Meyer [11] and Alvarez [2] stated that neither distention nor

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(Footnotes continued on next page)

contraction of a viscus will cause pain unless the mesentery is stretched. Using the dilatation of the pupil as an index of visceral afferent activity in cats anesthetized with chloralose (a compound of chloral hydrate and dextrose), Irving, McSwiney and Suffolk [12] stated that the threshold pressure for visceral afferent activity, after distention of the pylorus with a balloon, could be increased by at least 75 mm. of mercury by painting the pyloric mesenteries with cocaine. Brüning and Gohrbandt,[13] while admitting that traction on the mesenteries will cause pain, stated that distention of the viscus is the more important stimulus. The results of these experiments indicate that traction on the mesenteries can initiate visceral afferent activity and that the nervous activity resulting from the distention of a viscus may be due in part, or in whole, to traction on its mesenteries.

The great majority of workers believe that distention of a hollow viscus is a stimulus adequate for the production of pain (Brüning and Gohrbandt [13]; Fröhlich and Meyer [14]; Kappis [15]; McDowell [16]; Lebendenko and Brjussowa [10]; Alvarez [2]). Bloomfield and Polland [17] introduced balloons into the stomachs of human beings and inflated them with air. The intragastric pressures rose to and remained at 40 mm. of mercury, and discomfort and pain were felt by the subjects after 200 to 500 cc. of air had been introduced. Hurst,[18] Payne and Poulton [19] and Morley [3] expressed the belief that the pain which follows distention of a hollow viscus is caused by stretching of its sensory nerves. Spasm of the gastrointestinal musculature (Müller [20]; Ryle [21]; Fröhlich and Meyer [14]), as well as the increased tension on the muscular coat of a distended viscus (Hertz [22]), is thought to be stimulus adequate for the production of pain.

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POSSIBLE PATHWAYS FOR VISCERAL PAIN

Although the vagus nerve does contain visceral afferent fibers below the level of the diaphragm, it is generally believed that this nerve is not concerned with the transmission of pain from the abdominal portion of the alimentary canal (Langley [23]; Ranson [24]; Kappis [25]; Breslauer [8]; Alvarez [26]; Duschl [27]; Cannon [28]). The studies of Heinbecker and O'Leary [29] indicated that the vagus nerve, below the level of the diaphragm, is chiefly motor in function.

It is the consensus that the greater splanchnic nerve serves as the main pathway for painful impulses originating within the upper portion of the abdomen (Kappis [15]; Duschl [27]; Cannon [28]; Alvarez [2]). Ross [30] expressed the belief that the sensory fibers in the greater splanchnic nerve which supply the stomach are associated with the fourth, the fifth and, possibly, the sixth thoracic segment of the spinal cord, whereas Ranson and Billingsley [31] stated the opinion that the sensory fibers in the greater splanchnic nerve enter the spinal cord via the posterior roots of the sixth to the ninth thoracic spinal nerve. Edgeworth [32] stated that the large medullated (probably sensory) fibers originating in the abdominal viscera and traveling by way of the greater splanchnic nerve enter the spinal cord mainly through the posterior roots of the eleventh thoracic to the second lumbar spinal nerve. Bain, Irving and McSwiney [33] stimulated the central stump of the right greater splanchnic nerve in cats anesthetized with chloralose in which the spinal cord had been transected between the fifth and the sixth thoracic segment. Dilatation of the pupil, described by these workers as a very sensitive index of visceral afferent activity, was evident. However, after the right sympathetic trunk had been transected between the levels of the sixth and the seventh thoracic vertebra, stimulation of the right greater splanchnic nerve failed to cause dilatation of the pupil, although stimulation of the left greater splanchnic nerve was still effective. These investigators reported, further, that the spinal cord had to be transected at or above its third thoracic segment in order to eliminate, by transection of the spinal cord alone, the dilatation of the pupil caused by stimulation of the greater splanchnic nerve. These experiments indicate that some of the

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33. Bain, W. A.; Irving, J. F., and McSwiney, B. A.: The Afferent Fibers from the Abdomen in the Splanchnic Nerves, J. Physiol. **84**:323, 1935.

sensory fibers in the greater splanchnic nerve travel cephalad in the sympathetic chain and enter the spinal cord as high as its third thoracic segment. Cannon [28] reported that stimulation of the greater splanchnic nerve and of the upper lumbar portion of the sympathetic trunk is followed by actions which are indicative of pain.

Irving, McSwiney and Suffolk [12] stated that the threshold pressure for visceral afferent activity during distention of the stomach varied from 10 to 60 mm. of mercury. It appears from their experiments that the visceral afferent impulses initiated during distention of the stomach and during traction on the gastric and duodenal mesenteries reached the higher centers by way of both the vagus and the greater splanchnic nerve. Lebendenko and Brjussowa [10] found that the pain resulting from distention of the stomach of the dog could be abolished by a posterior rhizotomy extending from the fourth thoracic through the third lumbar level of the spinal cord. These investigators reported, further, that transection of the spinal cord at its fifth thoracic segment, bilateral transection of the sympathetic trunk at the level of the fifth rib and bilateral transection of the phrenic and vagus nerves did not abolish the pain produced by stretching of the gastric mesenteries. The investigators explained their inability to alleviate the pain produced by traction on the gastric mesenteries as due either to stimulation of the thoracic viscera by changes in pressure or to the presence of still another pathway for painful impulses, possibly associated with the aortic plexus.

MECHANISM OF REFERRED PAIN

Many theories have been proposed in an attempt to explain the neurologic mechanism of referred pain. Ross [30] was one of the first to state that a diseased organ gives rise to two types of pain, viz., a deeply seated pain located directly over the organ, and a more superficial, better localized pain in areas far removed from the site of the diseased viscus. This investigator proposed the theory (which was original with Stürge [34]) that irritation of the visceral terminations of the greater splanchnic nerve results in the passage of impulses to the posterior columns of the spinal cord, where they "diffuse" to the sensory fibers of the intercostal nerves. An "associated pain" is thus set up which is interpreted by the subject as having had origin along the distribution of the intercostal nerves which were involved. Head [35] suggested that the sensory and localizing powers associated with the body surface are far superior to those associated with the viscera. By what he termed a "psychical error of judgment," impulses which reach conscious levels from the "diffusion areas" of the spinal cord are interpreted by the person as having originated from the surface of the body rather than from the diseased viscus. Mackenzie [36] elaborated on Ross's theory of diffusion areas within the spinal cord. According to this worker, if the incoming nervous activity from the stimulated viscus diffuses onto and excites somatic afferent neurons, the subject interprets the pain as originating from the sensory terminals of the excited somatic neurons (the viscerocutaneous reflex). If, on the other hand, the incoming nervous activity diffuses onto and excites somatic efferent neurons, reflex rigidity of the somatic musculature innervated by that segment of the spinal cord results (the viscero-

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36. Mackenzie, J.: Some Points Bearing on the Association of Sensory Disorders and Visceral Disease, Brain **16**:321, 1893.

motor reflex). The sweating and pilomotor responses, frequently observed within areas of cutaneous hyperalgesia, were explained also by the concept of an "irritable focus."

Lennander [1] expressed the belief that referred pain is caused by stimulation of the sensory fibers of the somatic nerves by an irritated pleuroperitoneum, the latter resulting from contact with a diseased viscus. Morley [37] expressed the opinion that the dull, deep-seated pain located directly over a diseased organ results from tension on its walls, whereas the pain referred to the surface of the body is caused by irritation of the parietal peritoneum overlying the diseased viscus. According to this investigator, each somatic nerve supplies a strip of parietal peritoneum, the overlying skin and the intervening somatic musculature. Either nervous activity originating in the irritated peritoneum overlying a diseased viscus is misinterpreted as originating in the skin, or, what is more likely, there is actual diffusion of nervous activity within the spinal cord or the dorsal root ganglia from the sensory fibers supplying the peritoneum to the sensory fibers supplying the skin (the peritoneocutaneous radiation). The hypertonicity of somatic musculature, so frequently an accompaniment of referred pain, is brought about by activation of the anterior horn cells by nervous activity originating in the irritated peritoneum overlying the diseased viscus (the peritoneomuscular reflex).

Pollock and Davis [38] reported that the impulses initiated by the stimulation of the central diaphragmatic peritoneum traverse and enter the spinal cord over the trunk and the posterior roots of the phrenic nerves. Within the spinal cord, the impulses descend to the cells of the intermediolateral column of the eighth cervical and the first three thoracic segments. From this region the impulses travel through preganglionic sympathetic fibers, via the anterior roots, to the cervical sympathetic ganglia. These investigators stated:

> From here postganglionic fibers travel to the skin, blood vessels, meninges and other structures, where by some vasomotor (?) or hormonal (?) process the sensory endings of the cerebrospinal system are stimulated and a sensory impulse travels over the ordinary cerebrospinal system, enters the spinal cord through the posterior roots and ascends to consciousness.

Hinsey and Phillips [39] questioned the existence of the elaborate pathway proposed by Pollock and Davis for the transmission of pain produced by stimulation of the central diaphragmatic peritoneum. These investigators reported that such pain is dependent on afferent fibers contained in the phrenic nerve only and that it is independent of afferent fibers in the vagus and intercostal nerves and of efferent fibers in the sympathetic pathways.

Lewis and Kellgren [40] injected a hypertonic solution of sodium chloride into the first lumbar interspinous ligament of a human being and stated that the patient experienced the same character and distribution of pain that he had had previously during attacks of renal colic. It was concluded from this study that there exists no special form of pain, referred or otherwise, and no special form of viscerosensory or visceromotor reflexes which can be considered hallmarks of visceral disease. According to these investigators, a common system of afferent nerves supplies the deep somatic and certain visceral structures and is responsible for all of the pain and the referred phenomena associated with visceral disease.

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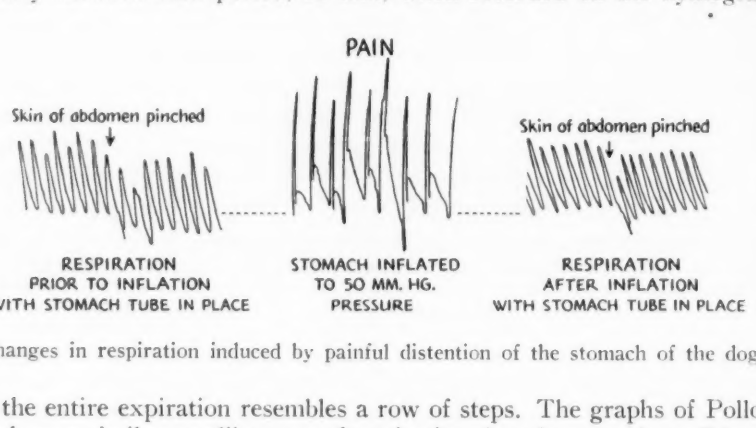
EXPERIMENTAL PROCEDURE AND RESULTS

It is the purpose of this paper to record the results of an investigation in which the pathways for pain from the stomach of the dog were determined by surgical methods.[41] Preliminary experiments indicated the necessity of a method for producing pain which was reproducible and in which the intensity of the stimulus could be calibrated accurately. The distention of the stomach with air by a balloon attached to a stomach tube and connected with an aneroid manometer proved to be satisfactory.

In the dog, it was found that a change in respiration was the only constant objective sign of the pain which follows distention of the stomach. This change was evident in the expiratory phase of respiration only and was of a peculiar steplike form (figure). Groaning and howling frequently accompanied the steplike form of expiration and aided in the final judgment as to whether or not the dog was experiencing pain.

The peculiar steplike form of expiration indicative of pain following distention of the stomach can be described as follows: The dog inhales deeply and quickly and then releases its breath in short spurts, or periods, of exhalation, halting momentarily between each period, so that, when recorded on the kymograph, the


PAIN
Skin of abdomen pinched
Skin of abdomen pinched
RESPIRATION PRIOR TO INFLATION WITH STOMACH TUBE IN PLACE
STOMACH INFLATED TO 50 MM. HG. PRESSURE
RESPIRATION AFTER INFLATION WITH STOMACH TUBE IN PLACE

Changes in respiration induced by painful distention of the stomach of the dog.

curve of the entire expiration resembles a row of steps. The graphs of Pollock and Davis [38] show a similar steplike type of expiration, but these workers did not indicate that it was regarded as a specific criterion of the presence of pain.

The apparatus used in the distention of the stomach consisted of a stomach tube, to the extremities of which were fastened a balloon and a T tube. A sphygmomanometer bulb, used to inflate the stomach, was attached to one arm of the T tube, and an aneroid manometer, calibrated in millimeters of mercury, was mounted on the other arm. The respiratory movements of the dog were recorded on smoked paper by placing on the dog's thorax a partially inflated rubber basketball bladder, which was connected to a tambour, on which was mounted a light aluminum stylus. The bladder was held in place by a metal arch, which was fastened to the sides of the table.

The actual procedure which has been employed in these studies can be illustrated by describing a typical experiment. A healthy dog of 10 to 15 pounds (4.5 to 6.8 Kg.) in weight was made to fast overnight, taken into a quiet room, fastened to the operating table and anesthetized with ether. When the stage of anesthesia was moderately deep, the stomach tube, with the balloon attached, was moistened with warm water and passed through the esophagus into the stomach. The dog was then allowed to breathe pure air until it responded, by a brief inhibition of respiration, to slight pinching of the skin of the abdominal wall. The balloon was then inflated rapidly by means of the sphygmomanometer bulb, and, as a rule, the intragastric pressure rose to about 35 or 40 mm. of mercury over a period of one to three minutes.

41. The suture material utilized in this experiment was furnished in part by Davis & Geck, Inc., Brooklyn.

The pressure usually remained at this level for an additional one-half minute, even though inflation was continued rapidly. In most cases the intragastric pressure then rose slowly to about 50 to 60 mm. of mercury, at which point the steplike expiration, indicative of pain, was evident (figure). The respiratory movements were recorded continuously throughout the experiment.

After establishment of the preoperative threshold for pain, one of a number of, or a combination of several, operative procedures was carried out (table). After enough time had elapsed for healing of the wound (this interval, which varied from one to three weeks, never reached the period required for regeneration of the transected nerves), the dog's stomach was again distended and its preoperative and postoperative thresholds for pain were compared. The postoperative threshold for pain was determined several times after each operation, a period of at least five days being permitted to elapse between inflations. Each animal was autopsied after its postoperative threshold had been established.

Since the animal's preoperative and postoperative thresholds for pain were recorded with the dog under light ether anesthesia, the question arose as to the possibility of error due to the influence of the anesthetic. The normal, or preoperative, thresholds were determined for 3 animals in the usual manner with the animal under ether anesthesia. Gastric fistulas were then constructed so that the stomach tube, with its attached balloon, could be inserted into the stomach directly without traversing the esophagus and in the absence of an anesthetic. The postoperative thresholds for pain were determined under these conditions and compared with the preoperative thresholds for the same dogs determined when they were under light ether anesthesia. The preoperative and the postoperative thresholds for pain were found to be practically identical. It is believed, therefore, that the state of anesthesia employed in these experiments had no effect on the thresholds for pain following distention of the stomach.

The question arose, also, whether or not a dog might become adapted to repeated distentions of its stomach and show progressively elevated thresholds for pain on subsequent inflations. Six dogs were subjected to such a procedure at frequent intervals for periods as long as seven months. No significant change in their thresholds for pain was observed.

It is conceivable that the venous and/or the arterial congestion within the stomach, resulting from the elevated intragastric pressure during distention of the organ, might alter the threshold for pain. As a test of this possibility, the veins draining the stomach were ligated in 2 dogs, and in 2 other dogs both the veins and the arteries were so treated. In no case was any difference evident between the preoperative and the postoperative threshold for pain following distention of the stomach.

Finally, the question arose as to the extent of the intragastric pressure required for secondary painful stimulation of the body wall and/or the structures and organs adjacent to the stomach. In 5 dogs the peritoneal cavity was distended with air by means of a hypodermic needle inserted through an anesthetized area of the abdominal wall. The peculiar steplike expiration, indicative of pain, appeared at pressures between 105 and 110 mm. of mercury in all cases. These experiments indicate that at intragastric pressures up to approximately 105 mm. of mercury the resulting pain is due to the distention of the stomach, whereas during intragastric pressures above this level the pain originates in the body wall and/or the structures adjacent to the stomach.

No significant change could be detected in the threshold for pain produced by distention of the stomach after either unilateral or bilateral transection of the vagus or the phrenic nerve in the cervical region or of the phrenic nerve within the thorax (table). Neither left unilateral nor bilateral transection of the sympathetic trunk just caudad to the origin of the greater splanchnic nerve (table) produced any change in the threshold for pain following distention of the stomach.

Dog No.	Operation	Preoperative Threshold, in Mm. Hg	Postoperative Threshold, in Mm. Hg
1	Transection of left vagus nerve in neck	47	54
2	Transection of left vagus nerve in neck	43	55
3	Transection of right vagus nerve in neck	63	45
2	Bilateral transection of vagus nerve in neck	43	45
23	Bilateral transection of vagus nerve in neck	60	50
132	Transection of right phrenic nerve in thorax	62	60
133	Transection of right phrenic nerve in thorax	55	60
133	Bilateral transection of phrenic nerve in thorax	55	55
68	Bilateral transection of phrenic nerve in neck	53	56
67	Bilateral transection of phrenic nerve in neck	50	48
72	Transection of left sympathetic trunk below splanchnic nerve	58	60
73	Transection of left sympathetic trunk below splanchnic nerve	60	56
108	Transection of left sympathetic trunk below splanchnic nerve	40	38
112	Transection of left sympathetic trunk below splanchnic nerve	50	58
128	Bilateral transection of sympathetic trunk below splanchnic nerve	55	60
72	Bilateral transection of sympathetic trunk below splanchnic nerve	58	55
129	Bilateral transection of sympathetic trunk below splanchnic nerve	55	58
134	Bilateral transection of sympathetic trunk below splanchnic nerve	55	58
33	Transection of spinal cord at C 8 - T 1	42	75
41	Transection of spinal cord at C 8 - T 1	40	No pain
42	Transection of spinal cord at T 1 - T 2	60	No pain
48	Transection of spinal cord at T 2 - T 3	45	90
45	Transection of spinal cord at T 3 - T 4	50	100
98	Transection of spinal cord at T 3 - T 4	55	120
49	Transection of spinal cord at T 4 - T 5	50	80
145	Transection of spinal cord at T 4 - T 5	55	80
159	Transection of spinal cord at T 5 - T 6	58	95
50	Transection of spinal cord at T 5 - T 6	50	55
146	Transection of spinal cord at T 5 - T 6	52	70
161	Transection of spinal cord at T 5 - T 6	60	60
75	Transection of spinal cord at T 7 - T 8	60	50
167	Transection of spinal cord at T 7 - T 8	55	55
166	Transection of spinal cord at T 8 - T 9	50	60
62	Transection of left splanchnic nerve	42	66
53	Transection of left splanchnic nerve	45	52
156	Transection of left splanchnic nerve	58	95
69	Transection of right splanchnic nerve	55	112
65	Transection of right splanchnic nerve	40	70
111	Transection of right splanchnic nerve	50	45
107	Transection of right splanchnic nerve	65	45
51	Transection of right splanchnic nerve	55	55
114	Transection of right splanchnic nerve	50	40
62	Bilateral transection of splanchnic nerve	42	83
69	Bilateral transection of splanchnic nerve	55	93
114	Bilateral transection of splanchnic nerve	50	80
107	Bilateral transection of splanchnic nerve	65	97
111	Bilateral transection of splanchnic nerve	50	92
156	Bilateral transection of splanchnic nerve	58	110
139	Transection of left rami communicantes, T 8 through T 13	60	72
160	Transection of left rami communicantes, T 8 through T 13	60	70
142	Transection of right rami communicantes, T 7 through T 13	50	85
138	Transection of right rami communicantes, T 8 through T 13	52	62
142	Bilateral transection of rami communicantes, T 7 through T 13	50	118
148	Bilateral transection of rami communicantes, T 8 through T 13	60	50
154	Bilateral transection of rami communicantes, T 8 through T 13	55	85
138	Bilateral transection of rami communicantes, T 8 through T 13	52	75
35	Transection of posterior roots, T 5 through T 9	60	67
83	Transection of posterior roots, T 3 through T 7	50	53
79	Transection of posterior roots, T 4 through T 7	40	50
89	Transection of posterior roots, T 5 through T 11	55	60
156	Transection of posterior roots, T 5 through T 13	50	78
133	Transection of posterior roots, T 6 through T 13	52	75
158	Transection of posterior roots, T 8 through T 12	55	100
155	Transection of posterior roots, T 7 through T 12	60	90
162	Transection of posterior roots, T 6 through T 11	55	90
89	Transection of posterior roots, T 5 through L 2	60	110
83	Transection of posterior roots, T 3 through L 3	52	105
136	Transection of posterior roots, T 9 through T 13	50	78
135	Transection of posterior roots, T 10 through L 4	55	72
135	Transection of posterior roots, L 1 through L 4	55	58
88	Transection of anterior roots, T 3 through T 6	50	40
96	Transection of anterior roots, T 4 through T 10	60	60
71	Transection of anterior roots, T 5 through T 11	60	58
94	Transection of anterior roots, T 4 through T 13	55	48
88	Transection of anterior roots, T 3 through T 13	50	58
94	Transection of anterior roots, T 4 through L 4	55	52
96	Transection of anterior roots, T 4 through L 4	60	52
130	Transection of anterior roots, T 10 through L 7	50	54
130	Transection of anterior roots, T 3 through L 7	50	50
121	Transection of anterior and posterior roots, T 4 through T 10	55	55
122	Transection of anterior and posterior roots, T 4 through T 10	45	50
122	Transection of anterior and posterior roots, T 4 through L 2	45	115
127	Transection of anterior and posterior roots, T 13 through L 4	60	58
152	Removal of left sympathetic trunk between 3d and 9th ribs	45	90
144	Removal of left sympathetic trunk between 4th and 9th ribs	55	55

Results of Determination by Surgical Methods of Pathways for Pain from the Stomach in Dogs—Continued

Dog No.	Operation	Preoperative Threshold, in Mm. Hg	Postoperative Threshold, in Mm. Hg
141	Removal of right sympathetic trunk between 3d and 9th ribs...	55	62
152	Removal of left sympathetic trunk between 3d and 9th ribs and right sympathetic trunk between 4th and 9th ribs.....	45	70
144	Bilateral removal of sympathetic trunk between 4th and 9th ribs	55	56
153	Removal of left sympathetic trunk between 3d and 10 ribs and right sympathetic trunk between 2d and 9th ribs.....	45	45
113	Transection of left intercostal nerve, T 4 through T 11, just distal to posterior div.....	30	35
118	Transection of left intercostal nerve, T 5 through T 12, just distal to posterior div.....	55	62
119	Transection of right intercostal nerve, T 5 through T 12, just distal to posterior div.....	55	50
120	Transection of right intercostal nerve, T 4 through T 11, just distal to posterior div.....	45	48
123	Bilateral transection of intercostal nerve, T 6 through T 12, just distal to posterior div.....	55	53
126	Bilateral transection of intercostal nerve, T 5 through T 12, just distal to posterior div.....	60	55
124	Bilateral transection of intercostal nerve, T 5 through T 12, just distal to posterior div.....	60	63
158	Bilateral transection of posterior roots, T 8 through T 12.....	55	100
158	Bilateral transection of posterior roots, T 8 through T 12, + transection of left sympathetic trunk below splanchnic nerve and at level of 6th rib.....	55	90
158	Bilateral transection of posterior roots, T 8 through T 12, + bilateral transection of sympathetic trunk below splanchnic nerve and at level of 6th rib.....	55	100
158	Bilateral transection of posterior roots, T 8 through T 12, + bilateral transection of sympathetic trunk below splanchnic nerve and at level of 6th rib + bilateral transection of greater splanchnic nerve.....	55	120

Unilateral transection of the left greater splanchnic nerve increased the thresholds for pain following distention of the stomach by an average pressure of 22 mm. of mercury, whereas unilateral transection of the right greater splanchnic nerve increased the thresholds for pain by an average of only 11 mm. of mercury (table). Bilateral transection of the greater splanchnic nerve in the same dogs, however, raised their thresholds for pain from an average preoperative level of 53 mm. to an average postoperative level of 93 mm. of mercury (table). These experiments indicate that the greater splanchnic nerve of the dog contains at least the greater majority of the afferent fibers which mediate pain following distention of the stomach. The left greater splanchnic nerve probably contains a greater number of these fibers than does the right.

Unilateral transections of the rami communicantes of the seventh or eighth through the thirteenth thoracic spinal nerve on the right side increased the thresholds for pain following distention of the stomach by an average pressure of 22 mm. of mercury, whereas the same operative procedure on the left side increased the thresholds for pain by an average pressure of only 11 mm. of mercury (table). We are unable to explain why these results are contrary to those of unilateral transection of the greater splanchnic nerve. Bilateral transection of these particular rami communicantes in the same dogs, however, raised the thresholds for pain from an average preoperative level of 52 mm. to an average postoperative level of 90 mm. of mercury (table). These results compare favorably with those obtained after bilateral transection of the greater splanchnic nerve.

Extensive bilateral transections of the posterior roots of the spinal nerves were performed on 3 dogs. In the first dog the posterior rhizotomies extended from the third thoracic through the third lumbar spinal nerves; those in the second dog, from the fourth thoracic through the fourth lumbar spinal nerves, and those in the third dog, from the fifth thoracic through the second lumbar spinal nerves (table). In each case the postoperative threshold for pain following distention of the stomach showed an increase of 50 mm. of mercury or more over the preoperative

level. A comprehensive series of experiments involving less extensive posterior rhizotomies were performed on 12 dogs (table). These experiments included posterior rhizotomies on the upper thoracic, the combined upper and middle thoracic, the middle thoracic, the combined middle and lower thoracic, the lower thoracic, the combined lower thoracic and upper lumbar and the upper lumbar nerves. It was found that the postoperative threshold for pain was elevated by at least 25 mm. of mercury provided that the posterior roots of the eighth through the thirteenth thoracic spinal nerve had been transected.

The spinal cords of 15 dogs were transected at different levels through the cervical and thoracic regions of the cord (table). The results of these experiments indicate that a chordotomy through any level of the spinal cord cephalic to its fourth thoracic segment will abolish completely the pain initiated by distention of the stomach. Transection of the spinal cord between its fourth and its seventh thoracic segment usually raised the threshold but seldom abolished completely the pain resulting from distention of the stomach. Chordotomy below the level of the seventh thoracic segment of the spinal cord had no effect on the threshold for pain following distention of the stomach.

The sympathetic trunk between the levels of the third or fourth and the ninth or tenth rib was removed unilaterally (table). Removal of the right sympathetic trunk, and in 1 of 2 cases removal of the left sympathetic trunk, did not affect the thresholds for pain following distention of the stomach. The second dog in which the left sympathetic trunk was removed showed, however, an increased threshold for pain amounting to a pressure of 45 mm. of mercury. Bilateral removal of these portions of the sympathetic trunk (table) provoked no change in the threshold for pain in 2 out of 3 dogs. The third dog, however, had a postoperative threshold for pain which was 25 mm. of mercury higher than its base line. In a few dogs the thickened portion of the sympathetic trunk, owing in all probability to the presence of afferent fibers from the greater splanchnic nerve, extends cephalad to the vicinity of the eighth rib. Should this portion of the sympathetic trunk be traumatized, one would expect an increase in the threshold for pain comparable to that resulting from damage to the greater splanchnic nerve.

Extensive bilateral transections of the anterior roots of the spinal nerves were performed in 3 dogs. In the first dog the anterior rhizotomies extended from the third thoracic through the seventh lumbar spinal nerve, whereas the operation in the second and third dogs extended from the fourth thoracic through the fourth lumbar spinal nerve (table). In no case was there any detectable difference in the preoperative and the postoperative threshold for pain.

Combined transections of the anterior and posterior roots of the thoracic and lumbar spinal nerves were performed in 4 dogs (table). In no instance did any of these animals show any change in their thresholds for pain other than what would be expected to follow transections of the posterior roots alone.

In 5 dogs, the lower seven intercostal nerves were transected unilaterally and bilaterally just distal to the point of origin of the posterior division of each nerve (table). These operative procedures appeared to have no effect on the thresholds for pain following distention of the stomach.

The following experiment was performed on 1 dog in an attempt to limit more closely the neurologic pathway which mediates pain from the stomach. Bilateral transections of the posterior roots of the eighth through the twelfth thoracic spinal nerve were performed. The threshold for pain, following this operative procedure, was increased by a pressure of 45 mm. of mercury. The threshold for pain continued at this level after bilateral transection of the sympathetic trunk at the level of the sixth rib and, again, just caudad to the origin of the greater splanchnic nerve.

After a bilateral transection of the greater splanchnic nerve, however, the threshold for pain increased by an additional pressure of 20 mm. of mercury. As has been stated elsewhere, it is necessary to transect the posterior roots of the fourth thoracic through the third lumbar spinal nerve in order to alleviate completely the pain which follows distention of the stomach in the dog. The results of the experiment just described would, therefore, indicate that the posterior roots of the sixth, seventh and thirteenth thoracic spinal nerves are capable of mediating a considerable portion of the pain resulting from distention of the stomach.

COMMENT

We believe that the peculiar steplike type of expiration which was observed in all dogs after distention of the stomach is an objective sign of the pain experienced by the animal. The presence of this sign following distention of the stomachs of dogs in which bilateral transections of the phrenic and vagus nerves and of the anterior roots of the thoracic and lumbar spinal nerves had been performed indicates that this sign is not dependent for its appearance on the phrenic nerve, the vagus nerve or the anterior roots of the thoracic and lumbar spinal nerves. It would appear, therefore, that this sign is not initiated by stress or embarrassment of the mechanism for respiration. When the spinal cord is transected cephalad to the fourth thoracic segment, the peculiar steplike type of expiration does not appear, except at intragastric pressures above approximately 105 mm. of mercury. This fact indicates that the sign is not the result of a spinal cord reflex and that it does depend for its appearance on higher centers in the central nervous system.

No significant changes in the thresholds for pain could be observed after repeated distentions of the stomach of the same dog over intervals as long as seven months. These observations indicate that adaptation of the stomach, under the conditions of this investigation, does not occur and bears no relationship to any increased postoperative threshold for pain. Gastric fistulas were constructed in one group of dogs, so that the stomach could be distended by an air-filled balloon in the absence of any anesthetic. The preoperative threshold for pain which was recorded while the dog was under very light ether anesthesia was identical with the postoperative threshold for pain recorded in the absence of any anesthetic. It is believed, therefore, that the state of anesthesia employed in this investigation does not alter materially the thresholds for pain following distention of the stomach. No change in the thresholds for pain was evident after ligation of the arteries and veins of the stomach. These results suggest that the threshold for pain following distention of the stomach is not affected by either venous or arterial congestion of that organ.

It is believed that the appearance of the peculiar steplike type of expiration following intragastric pressures at or above 105 mm. of mercury is due to pain which originates in the body wall and/or the structures and organs adjacent to the stomach. This is indicated by the results of an experiment in which the peritoneal cavities of 5 dogs were distended with air by means of a hypodermic needle inserted through an anesthetized area of the abdominal wall. The peculiar steplike type of expiration appeared in each case when the intra-abdominal pressure became elevated to between 105 and 110 mm. of mercury. It is believed, therefore, that the pain which follows intragastric pressures up to approximately 105 mm. of mercury originates in the stomach and its mesenteries.

Transection of the nerves containing the afferent fibers from the stomach should therefore raise the threshold for pain to a pressure of approximately 105 mm. of mercury, and it was by this means that the sensory pathway was traced. It should be pointed out, however, that the surgical method for tracing sensory pathways

is not adapted for estimating quantitatively the number of fibers mediating pain in any one nerve. It is distinctly possible that some nerve trunk might contain a few of the fibers mediating pain from an organ which, when all the remaining fibers of the pathway were intact, would conduct actually a relatively low percentage of the total number of the impulses initiated by the stimulation of the organ. If, on the other hand, these aberrant fibers were the only fibers of the pathway remaining intact, it is quite possible that they might deliver to the higher centers impulses in sufficient number to bring about the sensation of pain at the same threshold as it would have been produced had the entire pathway been intact. The investigations of Dusser de Barenne [42] indicate that under certain conditions neurologic mechanisms of this type do exist.

The results of the experiments already described indicate that in dogs the pain which accompanies distention of the stomach is mediated by afferent fibers which traverse the greater splanchnic nerve to the sympathetic trunk. The majority of these fibers probably enter the spinal cord via the rami communicantes and the corresponding posterior roots of the eighth through the thirteenth thoracic spinal nerve. This is indicated by the fact that transections of the rami communicantes or of the posterior roots of these nerves result in an elevation of the threshold for pain amounting to 25 mm. or more of mercury.

It has been noted that a more extensive posterior rhizotomy (extending from at least the fourth through the third lumbar spinal nerve) had to be performed in order to produce a maximal elevation of the threshold for pain after distention of the stomach (which was a pressure of approximately 105 mm. of mercury). This fact indicates that certain of the fibers which mediate pain from the stomach of the dog ascend and descend within the sympathetic trunk as far cephalad as the fourth thoracic and as far caudad as the third lumbar sympathetic ganglia. These ascending and descending fibers undoubtedly enter the spinal cord via the rami communicantes and the posterior roots of the fourth through the seventh thoracic and the first through the third lumbar spinal nerve. That these ascending and descending fibers are probably not of major physiologic importance when the rami communicantes and the posterior roots of the eighth through the thirteenth thoracic spinal nerve are intact is shown by the results of 3 experiments. In the first experiment, the sympathetic trunk was transected bilaterally just caudad to the origin of the greater splanchnic nerve from the sympathetic trunk; in the second experiment, the sympathetic trunk was transected bilaterally at the level of the sixth rib and again just caudad to the origin of the greater splanchnic nerve from the sympathetic trunk; in the third experiment, the sympathetic trunk was removed bilaterally between the levels of the third and the eighth or ninth rib. Elevation of the postoperative threshold for pain following distention of the stomach occurred in only 2 dogs of this group. We believe that these exceptions can be explained on the basis that in some dogs the thickened portion of the sympathetic trunk, undoubtedly caused by the presence of afferent fibers from the greater splanchnic nerve, extends cephalad to the vicinity of the eighth rib. Therefore, it is obvious that trauma to the thickened portion of the sympathetic trunk would produce changes in the threshold for pain similar to that following damage to, but not complete interruption of, the greater splanchnic nerve.

It was shown that the pain which follows dilatation of the stomach is obliterated by transection of the spinal cord at any level above its fourth thoracic segment. Successive transections of the spinal cord between its fourth and its seventh thoracic segment result in progressive lessening of the differences between the

42. Dusser de Barenne, J. G.: Central Levels of Sensory Integration, A. Research Nerv. & Ment. Dis., Proc. **15**:274, 1935.

preoperative and the postoperative threshold for pain. Transection of the spinal cord below the level of its seventh thoracic segment has no effect on the threshold for pain following distention of the stomach. This gradual diminution of the difference between the preoperative and the postoperative threshold for pain is due apparently to a progressive increase in the number of afferent fibers entering the spinal cord from the stomach as one progresses from the upper through the middle region of the thoracic portion of the spinal cord.

It is obvious from these observations that the results which were obtained after transection of the spinal cord are not in agreement with those obtained after transections of the posterior roots or of the rami communicantes of the eighth through the thirteenth thoracic spinal nerve. It has been stated elsewhere that transection of the posterior roots or of the rami communicantes of the eighth through the thirteenth thoracic spinal nerve is followed by an increase in the threshold for pain amounting to a pressure of 25 mm. or more of mercury. On the other hand, transection of the spinal cord caudad to the level of its seventh thoracic segment, an operative procedure which should interrupt any sensory pathway traversing the posterior roots or the rami communicantes of the eighth through the thirteenth thoracic spinal nerve, has no effect on the threshold for pain after distention of the stomach. Since the results of the various experiments already reported in this paper have indicated that thirteen posterior roots (fourth thoracic to third lumbar inclusive) contain sensory fibers mediating pain from the stomach, it is of interest to note that transection of the spinal cord caudad to its seventh thoracic segment fails to alter the threshold for pain, although only three of the original thirteen posterior roots, the fourth through the seventh thoracic, remain intact. Since transection of these posterior roots only is not associated with elevation of the threshold for pain, it is possible that certain peculiar circumstances may be attendant on a chordotomy which is performed immediately caudad to the seventh thoracic segment.

It is conceivable that these circumstances might lower the threshold for pain, by some mechanism local to the spinal cord, to such a degree that painful impulses, entering the spinal cord through the posterior roots of the fourth through the seventh thoracic spinal nerve, could reach the higher centers in sufficient numbers and strength to produce the sensation of pain when the stomach is distended to the level of its preoperative threshold for pain. We are unaware of any evidence in the literature or in the present studies which would prove this hypothesis, although the same general type of mechanism has been demonstrated by Dusser de Barenne.[42] This investigator showed that strychninization of a small portion of the posterior surface of one half of a segment of the spinal cord is followed by hyperesthesia in the entire dermatome supplied by the corresponding root. Furthermore, acute inflammatory states of the spinal cord, as might conceivably exist after chordotomy, are generally recognized as producing hyperalgesic states.

The weight of evidence shown by this investigation indicates that the afferent fibers which mediate the pain caused by distention of the stomach traverse the greater splanchnic nerve to the sympathetic trunk. These conclusions are in accord with the observations of Kappis [15] Lebendenko and Brjussowa,[10] Duschl,[27] Cannon [28] and Alvarez.[2] From the sympathetic trunk it would appear that the afferent fibers enter the spinal cord over one main and two subsidiary routes. The main route is via the rami communicantes and the posterior roots of the eighth through the thirteenth thoracic spinal nerve. Of the two subsidiary routes, the first, comprising the rami communicantes and the posterior roots of the fourth through the seventh thoracic spinal nerve, is probably of greater physiologic importance than is the second, consisting of the rami communicantes and the

posterior roots of the first through the third lumbar spinal nerve. Our observations relative to the entrance into the spinal cord of the sensory fibers from the greater splanchnic nerve are not in agreement with the conclusions of Ross [30] and of Ranson and Billingsley.[31]

Experiments carried out during this study have shown that neither the phrenic nor the vagus nerve is concerned with mediation of the pain which results from dilatation of the stomach in the dog. This conclusion agrees with the observation of Langley,[23] Kappis,[25] Breslauer,[8] Lebendenko and Brjussowa,[10] Duschl,[27] Alvarez [26] and Cannon.[28]

Davis and Pollock [43] stated that bilateral transection of the intercostal nerves relieved some of the pain which resulted from experimental distention of the gallbladder. They concluded from this observation that referred pain was probably present. In contrast to their observation, it has been shown in the present study that bilateral transection of the lower seven intercostal nerves in the dog did not change the threshold for the pain which follows distention of the stomach. It is our conclusion, therefore, that pain referred to the sensory terminals of somatic peripheral nerves does not exist in the dog after distention of the stomach. The absence of this type of pain seems even more likely since in no instance was it possible to discern areas of cutaneous hyperalgesia or of hypertonicity of somatic musculature after distention of the stomach. Furthermore, we were unable to elevate the threshold or abolish the pain following distention of the stomach by infiltrating the skin over the back and abdomen with procaine hydrochloride.

Weiss and Davis [44] expressed the belief that the intercostal nerves are of importance in the mediation of referred pain initiated by noxious stimulation of the viscera. These investigators studied the cutaneous areas to which pain was referred in 25 patients suffering from visceral disease; in addition, they studied normal persons in whom the esophagus and duodenum were distended with air-filled balloons. They reported that the sites of cutaneous pain could be abolished by infiltrating the skin with procaine and that unless the original sites of cutaneous pain were localized distinctly, the painful areas tended to shift to neighboring regions when the original sites were anesthetized. The experiments reported in the present paper offer no evidence in support of this conception.

According to Spameni and Lunedei [45] afferent fibers from the viscera enter the spinal cord and terminate on centrifugal neurons, which leave the spinal cord by way of the anterior roots and terminate in the sensory corpuscles within the skin. Impulses carried to the sensory corpuscles by these centrifugal neurons are thought to excite neighboring somatic afferent fibers, which, in turn, convey impulses to conscious levels, where they are interpreted as pain originating in the skin. Verger [46] stated that afferent impulses from a stimulated viscus enter the spinal cord and terminate on certain sympathetic neurons, which were said to leave the spinal cord by way of the posterior roots and to terminate on the "cutaneous vascular bouquets." Excitation of these particular sympathetic neurons supposedly modified the vascular bouquets in such a manner as to stimulate neighboring somatic

43. Davis, L., and Pollock, L. J.: Visceral Pain, Surg., Gynec. & Obst. **55**:418, 1932.

44. Weiss, S., and Davis, D.: The Significance of Afferent Impulses from the Skin in the Mechanism of Pain: Skin Infiltration as a Useful Therapeutic Measure, Am. J. M. Sc. **176**:517, 1928.

45. Spameni, P., and Lunedei, A.: Sui reflessi viscero-cutanei e sul mecanismo di produzione del dolore nelle affezione dei visceri e delle sierose, Riv. di clin. med. **28**:758, 1927; cited by Pollock and Davis.[38]

46. Verger, H.: Sur une modification due schème de Lemair pour la conception physiologique de réflexe viscéro-sensitif de Mackenzie, Gaz. hebd. d. sc. méd. de Bordeaux **43**:419, 1927; cited by Pollack and Davis.[38]

afferent neurons. These fibers, in turn, conveyed impulses to conscious levels which were interpreted as pain which had arisen within the skin. Wernøe [47] reported that a wide variety of viscerocutaneous reflexes can be observed after stimulation of various parts of the gastrointestinal tract. The experiments reported in the present paper offer no evidence in support of the ideas presented by these workers.

SUMMARY AND CONCLUSIONS

In this study an effort was made to outline the neurologic pathway for mediation of the pain which follows distention of the stomach in the dog. One hundred and fifty-eight dogs of 10 to 15 pounds (4.5 to 6.8 Kg.) in weight were employed.

Pain was produced by distending the stomach with an air-filled balloon. A method for graphically recording a constant response to the painful stimulus is described. This objective sign of pain, a peculiar steplike type of expiration, was shown to be independent of the vagus and phrenic nerves and of the anterior roots of the thoracic and lumbar spinal nerves. It was concluded from these observations that the sign is not initiated by stress or embarrassment of the mechanism for respiration. Evidence was presented that the sign was not dependent for its appearance on venous or arterial congestion of the stomach and that it did not involve a spinal cord reflex.

It was found that the respiratory index for pain in the dog on which no operation had been performed was evident when the intragastric pressure was elevated to 50 to 60 mm. of mercury. The threshold for this response remained constant for each animal which had not been operated on and did not change significantly after repeated inflations of the stomach for periods as long as seven months.

The results of this investigation indicate that visceral afferent nerve fibers only are involved in the mediation of the pain which follows distention of the stomach in the dog and that they are contained within the greater splanchnic nerve. The majority of these fibers traverse the rami communicantes of the eighth through the thirteenth thoracic spinal nerve and enter the spinal cord through the corresponding posterior roots. Evidence was presented which indicates that some of these fibers traverse the sympathetic trunk as far cephalad as the fourth thoracic and as far caudad as the third lumbar sympathetic ganglion. These particular fibers undoubtedly enter the spinal cord over the rami communicantes and the corresponding posterior roots of the fourth through the seventh thoracic and the first through the third lumbar spinal nerve.

We were unable to elevate the threshold or abolish the pain following distention of the stomach by infiltrating the skin over the back and abdomen with procaine or by performing bilateral transections of the lower seven intercostal nerves and of the anterior roots of the thoracic and lumbar spinal nerves. In no case were we able to discern areas of cutaneous hyperalgesia or of hypertonicity of somatic musculature following distention of the stomach. It is our conclusion, therefore, that pain referred to the sensory terminals of somatic peripheral nerves does not exist in the dog after distention of the stomach.

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47. Wernøe, T. B.: Viscero-cutane Reflexe, Arch. f. d. ges. Physiol. **210**:1, 1925.

FORMATION OF DEMYELINATED PLAQUES ASSOCIATED WITH CEREBRAL FAT EMBOLISM IN MAN

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This presentation is concerned with a detailed histopathologic study of the cerebral lesions associated with fat embolism. Their analysis revealed certain similarities to the early focal lesions of demyelination occurring in cases of disseminated sclerosis.

REPORT OF CASES

CASE 1.—*History.*—A 20 year old white man, a student, had been struck by an automobile one hour before admission to the hospital. Roentgen studies revealed comminuted fracture of the middle third of the left tibia and fibula. The previous history was normal.

On the morning of admission (1 a. m.) the patient was alert, and the results of physical examination were normal except for fracture of the left leg. He failed to respond during early morning care, and an hour later he could not be aroused for breakfast. He never regained consciousness. Urinary and fecal incontinence was noted. The temperature was 101.6 F., the pulse rate 100, the respiratory rate 26 and the blood pressure 114 systolic and 90 diastolic. Supraorbital pressure failed to arouse him. The pupils were moderately contracted and responded slightly to light. There was spontaneous nystagmus. Examination of the eyegrounds revealed no abnormality. Both upper extremities were spastic, the left more so than the right. The achilles and patellar reflexes were more active on the right, and there was a Babinski response on that side.

On the third day in the hospital a diffuse, petechial hemorrhagic rash developed in the skin over the axillas, chest, abdomen, flanks and groins. Cheyne-Stokes breathing was observed. The patient died on the fifth day.

General Autopsy.—The skin of the entire body presented an enormous number of minute, punctate hemorrhagic lesions. Lesions of similar appearance were seen in the heart muscle, peritoneum, liver, spleen and kidneys. Gentle pressure on the cut surface of the lung caused a few small fat droplets to exude. Microscopic sections of the skin and of all the viscera prepared by the special technic with osmic acid and sudan III showed capillaries plugged with fat droplets. The accumulations of fat were most abundant in the lung.

Gross Examination of Brain.—Throughout the gross sections of the brain there were observed multiple pink points, ranging from the size of a pinpoint to 2 mm. in diameter. They were scattered throughout the white and the gray matter indiscriminately, though they were more prominent in the white (fig. 1). Inferiorly both caudate nuclei were softened; the area of this gross change measured 6 to 8 mm. in diameter. In the medial extent of the right caudate nucleus there was a hemorrhagic area, measuring 3 mm. in diameter. There were marked congestion of the blood vessels and some perivascular hemorrhage.

Microscopic Study of Brain.—Sections from several cortical areas, the midbrain, the medulla and the cerebellum were stained with hematoxylin and eosin and cresyl violet and by the Loyez myelin sheath, the Bodian 1 per cent protargol (strong protein silver) and the scarlet red method.

Histologic examination revealed two types of abnormalities, which were sometimes combined and sometimes observed separately. An interesting manifestation was the presence of circumscribed, diffusely disseminated patches of demyelination, throughout the brain substance, most prominent in the subcortical areas. Analysis of the histologic structure of these lesions revealed two distinct types: (*a*) Circumscribed areas of focal necrosis characterized by complete cellular destruction, loss of myelin sheaths and nerve fibrils and rarefaction of the tissue. These areas of degeneration contained no cellular elements except a few histiocytes. There were no fat granule cells and no inflammatory reaction. The majority of these foci suggested a perivascular distribution. Usually they contained a central capillary plugged with

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fat droplets (fig. 2). These lesions may be classified as an acute form of necrosis resulting from sudden interruption of the blood supply by the fat embolus. (*b*) Lesions characterized by destruction of myelin sheaths (figs. 3 and 4), partial preservation of axis-cylinders (fig. 5) and an early stage of repair, consisting of glial cell proliferation (fig. 7).

Axonal changes are illustrated in figures 5 and 6. The neurofibrils were swollen and thickened, with irregular beading, and intensely stained. In the central part of the patch, which contained the more extensively deteriorated tissue, the nerve fibrils revealed more advanced lesions in the form of fragmentation and poor impregnation (fig. 5). Some nerve fibers were broken into granular debris or were undergoing vacuolation. This advanced altera-

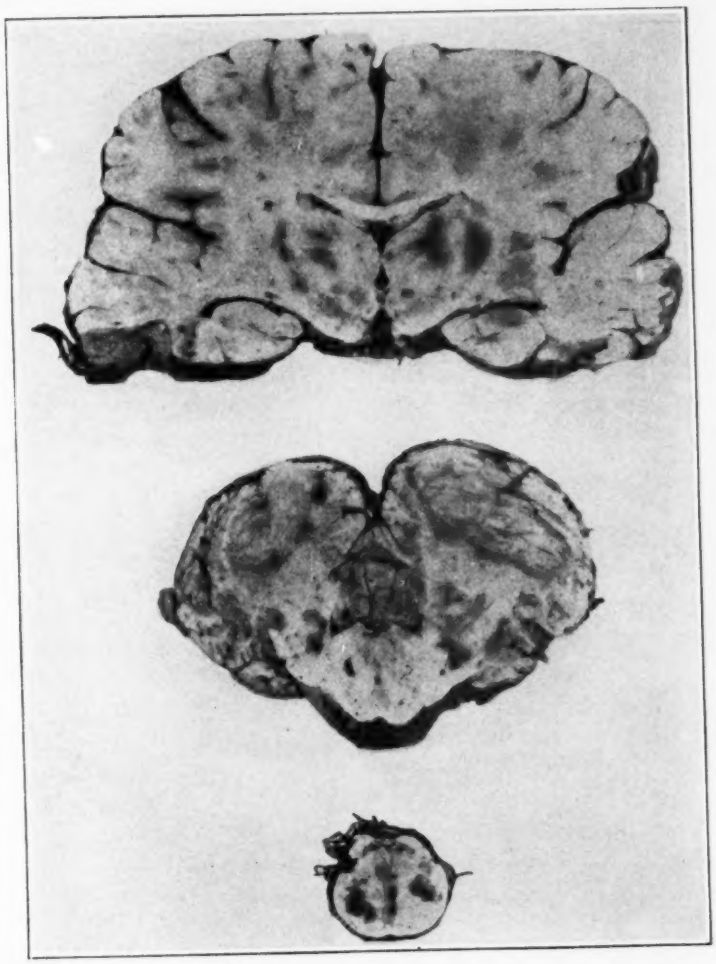

Fig. 1 (case 1).—Petechial hemorrhages scattered throughout the white and gray matter.

tion of the nerve fiber was observed only occasionally. As a rule the axis-cylinders were preserved and showed a relative increase in size of either isolated axons or groups of axons unassociated with any other obvious change. The swollen fibers in transverse section appeared circular, granular or homogeneous (fig. 6); the outline of the large fibers was often irregular.

Loyez and Spielmeyer myelin sheath preparations revealed complete disappearance or extensive degeneration of myelin in the majority of the patches (figs. 3 and 4). Occasionally a small number of myelin sheaths were preserved; they were irregular in outline and frequently were broken up into globules. These areas of demyelination resembled the lesions in cases of multiple sclerosis which Spielmeyer described as shadow patches (*Markschattenherde*).

A striking manifestation of the process was the presence of early stages of glial repair in some of the areas of demyelination. The cell stain revealed the presence of compact accumulations of glia cells. These cells usually varied considerably in size and shape (fig. 7). With the Cajal gold chloride-mercury bichloride stain the majority showed the characteristic structure of glia cells. There was a slight accumulation of microglia about the margin of some of the patches of demyelination. The nerve cells in some of the areas of demyelination were well preserved (fig. 7). A slight perivascular accumulation of round cells was present occasionally in the tissue surrounding the patches.

The changes in the cerebral capillaries and their relationship to the disseminated focal lesions deserve special attention. Specific stains (scarlet red) revealed numerous fat emboli

Fig. 2 (case 1).—Demyelinated plaque, with a central capillary plugged with a fat embolus. Spielmeyer myelin sheath stain; × 100.

in the majority of the capillaries situated in or about the patches of demyelination. Only occasionally were the latter avascular. It is likely that an associated blood vessel would have been found in each if serial sections had been made.

What appeared to be small punctate hemorrhages to the naked eye were recognized as conglomerations of numerous ring hemorrhages with low power magnification. They presented a clear, pale-stained center surrounded by a large ring of extravasated blood. The center usually contained a capillary plugged with fat (scarlet red) and surrounded by an area of necrotic tissue. These hemorrhages were probably due to obstruction of the lumens of the blood vessels by fat emboli; in other words, they were hemorrhagic infarcts.

CASE 2.—*History.*—A white man aged 62 was admitted to the hospital unconscious a few hours after he had been struck by an automobile. He had suffered compound fractures of the right tibia, the pelvis and the fourth and fifth fingers of the right hand. On the day of admission reduction and closure of the compound fractures of the tibia and amputation of the fifth finger were performed. After operation the patient was deeply cyanotic and gasping for breath. The respiratory rate hovered between 56 and 60 per minute. Roentgen ray examination of the chest revealed elevation of the diaphragm on the left and evidence of bronchopneumonia on the right. In spite of oxygen therapy the cyanosis persisted. The

Fig. 3 (case 1).—Perivascular area of demyelination with partly preserved myelin sheaths ("myelin shadow" plaque). Spielmeyer myelin sheath stain; × 100.

patient died forty-eight hours after admission. Clinically, the diagnosis of pulmonary or cerebral fat embolism was considered.

General Autopsy.—Autopsy revealed a comminuted fracture of the lower third of the right tibia and compound fractures of the fourth and fifth fingers of the right hand. There were partial collapse and acute passive congestion of the lungs.

Gross Study of Brain.—The majority of the coronal sections of the brain revealed disseminated lesions similar to those described in case 1. In many of the sections there was pronounced congestion of the vessels, which were frequently surrounded by small peri-

vascular hemorrhages. The rostral sections of the brain stem and cerebellum contained diffusely scattered, pinpoint, pinkish spots of discoloration.

Microscopic Study of Brain.— Sections from the frontal, parietal, temporal and occipital lobes of both hemispheres and from the basal ganglia, the brain stem and the cerebellum were stained with hematoxylin and eosin and cresyl violet and by the Loyez, Spielmeyer, Bodian and scarlet red methods. Microscopic examination revealed disseminated areas of demyelination and the presence of small hemorrhages similar to those described in case 1. A detailed description will therefore be omitted, though, again, attention should be drawn to their similarity to focal lesions observed in cases of acute multiple sclerosis.

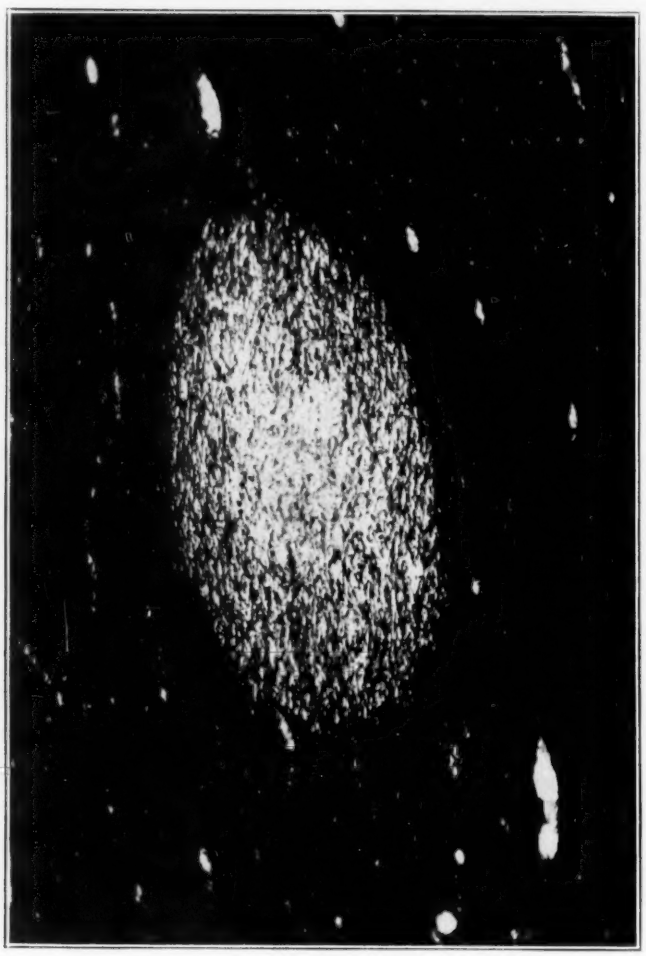

Fig. 4 (case 1).—Demyelinated plaque with preservation of numerous beaded and thinned myelin sheaths. Spielmeyer myelin sheath stain; × 100.

Myelin sheath preparations revealed diffusely scattered, circumscribed areas of focal demyelination throughout the brain substance, most prominent in subcortical areas. They usually contained no cellular elements except for a few glial nuclei. The majority of the patches of demyelination appeared to be perivascular (fig. 8). They showed a central capillary completely occluded by fat globules. These circumscribed lesions appeared to be of different ages, the myelin being completely removed in some sections while in others swollen and fragmented myelin sheaths were still present. Bodian protargol preparations revealed partial preservation of the neurofibrils, although to a lesser degree than in case 1. Many of the remaining fibrils appeared swollen. Some of the lesions were devoid of cellular elements, representing complete degeneration and necrosis of all nerve elements. Here the tissue was

meshlike, and there was no proliferation of glia or capillaries. The latter lesions had all the characteristics of miliary, anemic infarcts.

Sections stained with scarlet red demonstrated the presence of fatty emboli in the capillaries and small veins. These oval globules sometimes occupied the entire lumen of the vessel. The fat emboli were most numerous within the areas of demyelination.

In addition to the disseminated patches of demyelination, the cerebral tissue showed two types of diffusely scattered punctate hemorrhages, the so-called ring hemorrhage and the perivascular hemorrhage. The ring hemorrhage usually consisted of a central capillary plugged with fat and surrounded by a small area of degenerated tissue, around which there was a

Fig. 5 (case 1).—Irregular swelling of axis-cylinders at the periphery of a plaque, with poor impregnation and fragmentation of the nerve fibrils in the center of the lesion. Bodian silver impregnation; × 122.

large ring of red blood cells (fig. 9). The second type, the so-called perivascular hemorrhage, consisted of small arterioles and capillaries engorged with blood and surrounded by large masses of red blood cells limited to the distended perivascular spaces, some of which had been so distended that rupture and extravasation of red blood cells into the surrounding brain parenchyma had occurred. There was no indication of inflammatory reaction. The vessel walls exhibited no structural change.

Summary of Pathologic Changes.—It appears that the most constant and uniform pathologic change in the brain associated with fat embolism consists of

scattered, circumscribed areas of demyelination and necrosis. The focal areas of degeneration were of different ages and different structure.

Three types of focal lesions have been described: (1) Circumscribed areas of necrosis characterized by complete cellular destruction and loss of myelin sheaths and nerve fibrils, associated with rarefaction of the tissue. These areas usually contained a central capillary completely occluded by a fat embolus. (2) Lesions characterized by partial preservation of the nerve parenchyma and early signs of

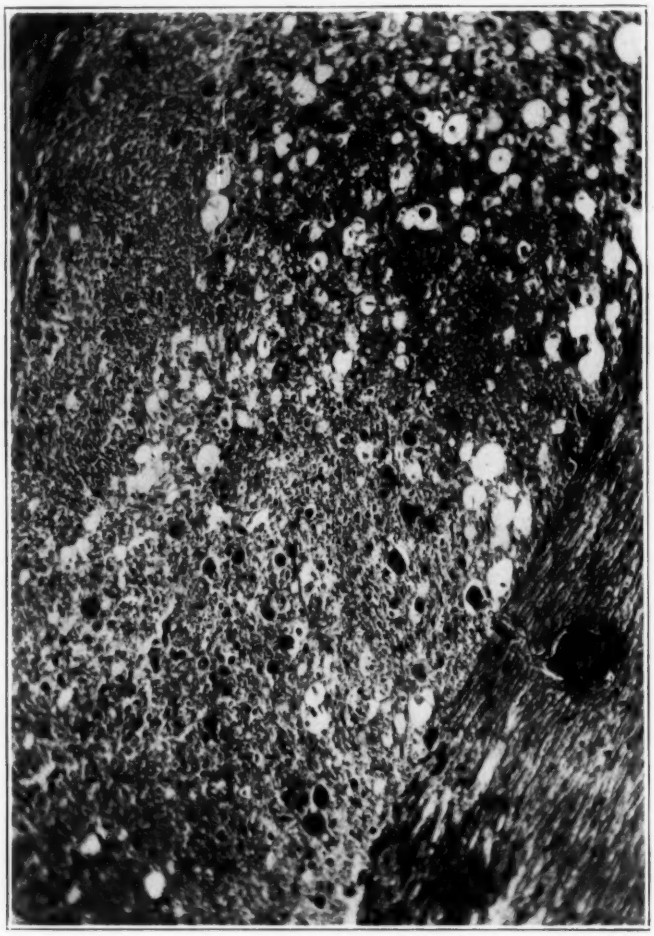

Fig. 6 (case 1).—Enormously swollen axis-cylinders in transverse section. Bodian silver impregnation; × 122.

glial repair. These areas were similar to the early lesions of multiple sclerosis.[1] (3) So-called ring hemorrhages, consisting of a central capillary plugged with fat and surrounded by an area of necrotic tissue and a large ring of red blood cells. The last lesion is among the most common changes associated with cerebral fat embolism and may be considered as a minute hemorrhagic infarct.

1. Scheinker, I. M.: Histogenesis of the Early Lesions of Multiple Sclerosis: I. Significance of Vascular Changes, Arch. Neurol. & Psychiat. **49**:178-185 (Feb.) 1943.

COMMENT

The three types of focal lesions have in common alteration of the blood supply by the embolic occlusion of the capillaries. Their differences might be explained by variation in the rapidity and completeness of the occlusion, by the nature and size of the occluded blood vessel and by the "local factor" (Spielmeyer). It seems proper to assume that the degree of tissue damage may be dependent on the degree of focal cerebral hypoxia resulting from the circulatory disturbance. Whereas

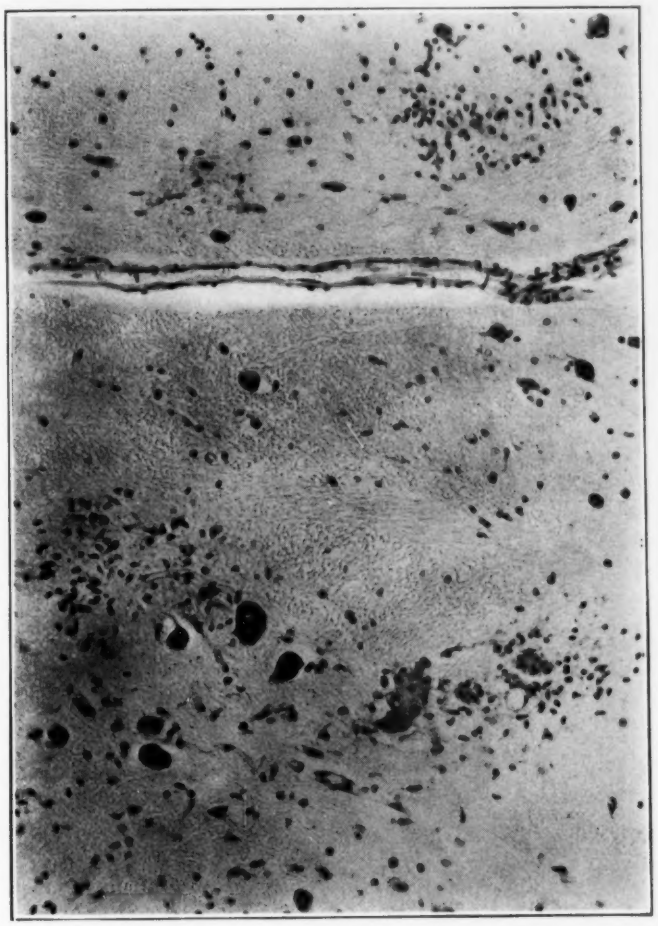

Fig. 7 (case 1).—Beginning of glial repair in the form of proliferation of glia cells. Note the preservation of cells of the basal ganglia. Cresyl violet; × 100.

the devastating lesions might be interpreted as acute tissue destruction due to a sudden and complete interruption of the blood supply by the fat embolus, lesions of lesser severity may be due to slower development of, or less complete, circulatory embarrassment. Whereas with severe hypoxia the glia perishes together with the nerve parenchyma, in milder states of hypoxia there occurs relatively mild destruction of tissue limited particularly to the myelin sheaths. The nerve parenchyma and the supportive glia are partly preserved. The glia, though affected, is capable of proliferation, producing changes similar to those of the "early" lesions of dis-

seminated sclerosis.[1] If the morbid process were prolonged by survival of the patient, the glial proliferation probably would be replaced by proliferation of glial fibrils, and a true "sclerosis" would result.

Relatively few areas of tissue destruction were present in the cortex, though it contained many areas in which fat emboli were present. Probably the capillary anastomoses are so extensive that the nutrition of the tissue was only slightly impaired, if at all. In the white matter, where the capillary network is not so

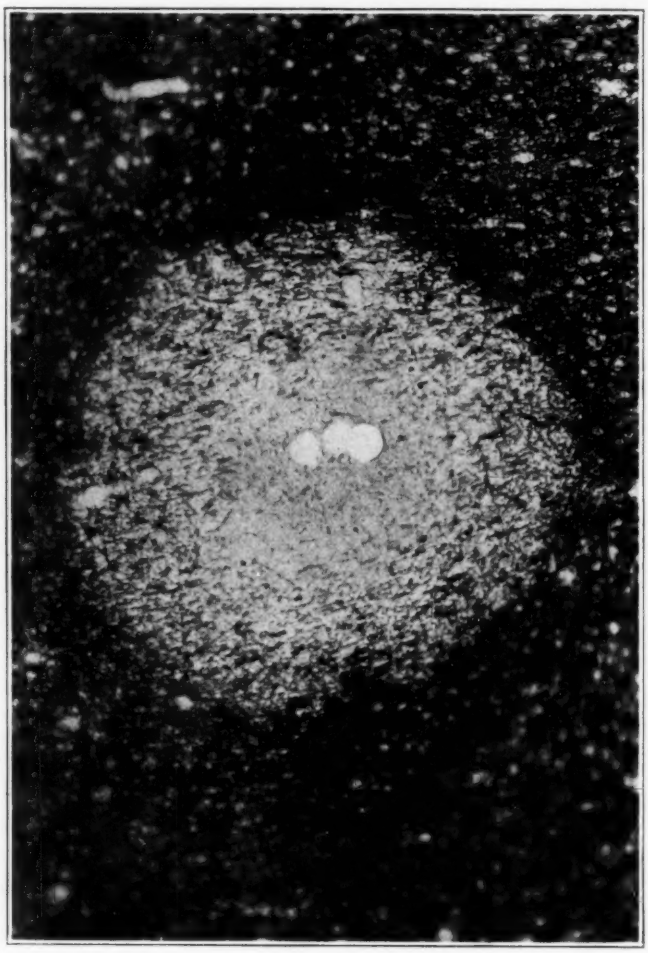

Fig. 8 (case 2).—Perivascular patches of demyelination with central capillaries. Spielmeyer myelin sheath stain; × 100.

extensive, the tissue damage was more severe and the number of necrotic areas more numerous.

Considerable difference of opinion exists as to the origin of ring hemorrhages. Frauendorfer [2] attributed the hemorrhage to rhexis of the blood vessel wall because of pressure from the embolus. Vance [3] and Winkelman [4] expressed the opinion that the ring hemorrhage represented a microscopic hemorrhagic infarct.

2. Frauendorfer, O.: Ueber Fettembolie, Beitr. z. gerichtl. Med. **6**:1, 1924.

It is surprising that in spite of the existence of a voluminous literature dealing with fat embolism (there are over five hundred references at present) the changes in the nervous system seldom have been described in detail. An adequate review of the literature on fat embolism has been made by Winkelman.[4] In his own cases Winkelman described the presence of two types of lesions, the ring hemorrhage and the small areas of necrosis termed "rarefied areas." He noted in some areas of necrosis "repair by gliosis and vascularization." His figure 8 illustrates

Fig. 9 (case 2).—Ring hemorrhages with central capillaries. Hematoxylin and eosin stain; × 100.

beautifully beginning sclerosis around an occluded blood vessel. Vance,[3] in his description of the early stage of the necrotic areas, mentioned the "preservation of the axis cylinders . . . Later the process of repair sets in and glial cells tend to fill in the spaces."

3. Vance, B. M.: The Significance of Fat Embolism, Arch. Surg. **23**:426-465 (Sept.) 1931.

4. Winkelman, N.: Cerebral Fat Embolism, Arch. Neurol. & Psychiat. **47**:57-76 (Jan.) 1942.

SUMMARY

In a clinical and pathologic consideration of cerebral fat embolism, emphasis is placed on the diffusely scattered patches of demyelination, which are considered to be a constant and striking histopathologic feature of the disease.

The lesions of cerebral fat embolism are of two varieties: (*a*) miliary anemic infarcts, which result in focal areas of necrosis (destruction of all tissue elements), and (*b*) focal areas of demyelination with partial preservation of the nerve parenchyma (nerve cells and nerve fibrils) and early signs of glial repair.

The lesions of cerebral fat embolism are considered to be similar to the early lesions of multiple sclerosis.

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OCCLUSION OF THE ANTERIOR INFERIOR CEREBELLAR ARTERY

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The clinical picture which follows occlusion of the anterior inferior cerebellar artery is probably the least known of any of the cerebellar artery syndromes. To my knowledge only 1 such case has been reported, that of Goodhart and Davison.[1] Therefore, it seems worth while to record permanently the following case because of the clarity of the symptoms and the precise anatomic localization of the lesion.

ANTERIOR INFERIOR CEREBELLAR ARTERY (MIDDLE CEREBELLAR ARTERY)

This is probably the most variable of the cerebellar arteries. It usually originates as a branch of the basilar artery about 1 cm. above the junction of the two vertebral arteries, but it may arise either from the vertebral or from the basilar artery by a common trunk with the posterior inferior cerebellar artery. The course of the artery is obliquely backward and downward beneath the seventh and eighth cranial nerves and the flocculus of the cerebellum, where it divides into many branches which supply the anterior and inferior surfaces of the cerebellum. As it traverses the restiform body, the middle cerebellar peduncle and the flocculus, it supplies small branches to these structures. The lateral part of the biventral lobule, the flocculus and the inferior and superior semilunar lobules of the cerebellum thus receive their blood supply from this source. There are abundant anastomoses with the posterior inferior and superior cerebellar arteries.

REPORT OF A CASE

History.—One morning, soon after arising, the patient, a man aged 48, suddenly experienced dizziness, as if the room were turning from the right to the left. After this he had tinnitis, nausea and vomiting, and about two hours later he noticed that the right side of his face was paralyzed, so that he could not close his right eye or speak distinctly. He remained in bed during the next seven days because of weakness, dyspnea and slight dizziness. Then, after much persuasion, he agreed to enter the hospital.

At the age of 8 years the patient had had an "abscess of the spine," which left him with a crooked back and deformity of the chest. For the past two or three years he had been unable to work because of headaches, weakness and dyspnea, which were ascribed to high blood pressure.

Examination.—On admission the temperature was 98.6 F., the pulse rate 100, the respiratory rate 28 and the blood pressure 230 systolic and 150 diastolic. The patient was lethargic and irritable and was moderately confused. There was thoracic kyphoscoliosis, which made examination of the chest difficult. The heart was enlarged to the left; the cardiac rhythm was normal, and the aortic second sound was accentuated. There were moist rales throughout both pulmonary fields. The right pupil was 2 mm. in diameter and the left one 3.5 mm.; both reacted well to light and in accommodation and convergence. There were ptosis of the right eyelid and slight enophthalmos of the right eye. The retinal arteries were sclerotic and the optic disks slightly blurred. Visual acuity and the visual fields were normal, and extraocular movements were well performed. The right side of the face, including the orbicularis oculi and frontalis muscles, was completely paralyzed. On the right side there was complete nerve deafness and on the left side slight impairment of auditory acuity. Well sustained nystagmus

From the Department of Neurology, Harvard Medical School, and the Neurological Unit, Boston City Hospital.

1. Goodhart, S. P., and Davison, C.: Posterior Inferior and Anterior Inferior Cerebellar Arteries, Arch. Neurol. & Psychiat. **35**:501 (March) 1936.

appeared on both right and left lateral gaze and left rotary nystagmus on upward gaze. Pain and temperature sensations over the right side of the face were greatly impaired, and over the right cheek there was also slight impairment of light touch sensation. The right corneal reflex was hypoactive. Speech was somewhat indistinct, but no dysphonia or dysphagia was noted. There was cerebellar ataxia in the use of the right arm and leg. Movements were slow and awkwardly executed; in performing the finger to nose and heel to knee tests there were dysmetria and intention tremor. The right arm was hypotonic, and Holmes's rebound sign was elicited. Gait and station could not be tested. Pain sensation was inconstantly diminished over the left side of the neck and left upper extremity, but not definitely so over the rest of the body. Muscles were equally strong on the two sides of the body. Tendon reflexes were equally active, and plantar responses were bilaterally flexor.

Laboratory Data.—Urinalysis revealed a 1 plus reaction for albumin, a specific gravity of 1.012 and an occasional granular cast in the sediment, but no red or white blood cells. The white blood cell count was 18,200. The electrocardiogram showed ectopic auricular rhythm

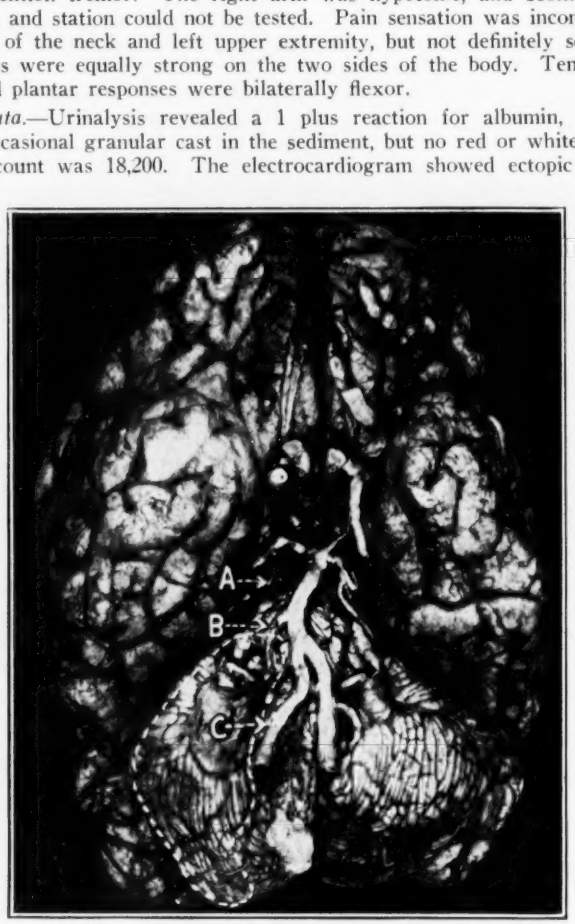

Fig. 1.—Photograph of the brain, showing (*A*) the right superior cerebellar artery, (*B*) the right anterior inferior artery and (*C*) the right posterior inferior artery. The dotted area includes the zone of recent infarction.

and left axis deviation. The cerebrospinal fluid showed an initial pressure of 170 mm., 122 mg. of protein per hundred cubic centimeters, 6 lymphocytes per cubic millimeter and negative Wassermann and Hinton reactions.

Course.—Despite treatment for congestive heart failure, the patient failed to improve. In the succeeding days he became more inattentive, confused and disoriented. The neurologic examination was repeated several times, with about the same results as those already recorded. During the fourth week of the illness the patient's temperature rose to 101 F., and signs of pulmonary congestion appeared. He died two days later, on the twenty-fifth day of the illness.

Anatomic Diagnosis.—The anatomic diagnosis referable to the brain was cerebral arteriosclerosis and encephalomalacia; thrombosis of the right anterior inferior cerebellar artery, with infarction of the lateral part of the medulla oblongata and cerebellum; thrombosis of the lateral branch of the left posterior inferior cerebellar artery, with infarction of the cerebellum, and multiple small softenings in the basis pontis, the midbrain and the lenticular nuclei.

Other conditions were: arteriosclerotic and hypertensive heart disease, healed bilateral pyelonephritis, benign prostatic hypertrophy and tuberculous spondylitis (?).

Gross Pathologic Changes.—The vertebral, basilar, cerebellar and cerebral arteries were the seat of marked atheromatous change. There was an anomaly of the circle of Willis; the left posterior cerebral artery arose from the internal carotid artery and the right posterior cerebral artery from the basilar artery. The right anterior inferior cerebellar artery was completely occluded by an atheromatous plaque at the point of its origin from the basilar artery. The lateral branch of the left posterior inferior cerebellar artery was also occluded. The right flocculus and the biventral and superior and inferior semilunar lobules of the cerebellum were softened. The restiform body and brachium pontis on the right side felt less firm than those on the left. On the inferior surface of the left cerebellar hemisphere, involving chiefly the inferior semilunar lobule, was a triangular depression, 2 cm. in its widest portion and 0.5 cm. deep, where the cerebellar cortex and the subcortical white matter had been destroyed (fig. 1).

Section of the brain, after fixation in formaldehyde, showed a well demarcated area of recent softening in the right side of the cerebellum and bulb. In addition several small cystic defects, all less than 0.5 cm. in diameter, were observed in the right centrum semiovale, the anterior limb of the right internal capsule and the basis pontis on the right side.

Fig. 2.—Lower pontile level.

Microscopic Pathologic Changes.—The medulla, pons and cerebellum were sectioned serially and stained by the Weil and Nissl methods.

Level of the Midpons: This region appeared to be the highest level of the infarction. The area of necrosis was small and involved only part of the brachium pontis and some of the fibers of the right trigeminal nerve.

Level of the Nucleus of the Sixth Nerve: The right middle cerebellar peduncle, including the region of the restiform body, the spinal nucleus and tract of the right trigeminal nerve and the lateral portion of the right lateral vestibular nucleus were destroyed. In the nucleus of the right seventh nerve there was "axonal reaction" of the nerve cells, and a similar reaction was observed in the left pontile nuclei. A few of the folia of the cerebellar cortex adjacent to the pons were necrotic (fig. 2).

Level of Junction of Pons and Medulla: The right eighth nerve, the ventral and dorsal cochlear nuclei, the spinal nucleus and tract of the right trigeminal nerve, the lateral portion of the right spinal vestibular nucleus and the restiform body were all degenerated. The lesion also involved the ventral spinocerebellar tract.

Level of Midolivary Region: The lateral portion of the medulla oblongata, including the fibers of the ninth and tenth nerves and the nucleus ambiguus, was intact. The only lesion at this level was situated in the right restiform body. The nerve cells in the left inferior olivary nucleus were undergoing "axonal reaction"; many of the cells had disappeared and were replaced by foci of glia cells.

Level of Inferior Pole of Olive: Except for descending degeneration of the spinal tract of the right fifth nerve, there were no definite lesions of this level (fig. 4).

There was an advanced degree of hyperplastic arteriolosclerosis and atherosclerosis of the larger arteries. The areas of necrosis were replaced by microglial phagocytes, and in the adjacent tissues astrocytes were increased in number and size.

Fig. 3.—Upper bulbar level.

Fig. 4.—Midolivary level.

COMMENT

The clinicoanatomic correlation in this case is too obvious to require detailed comment. Suffice it to mention that the palsies of the seventh and eighth cranial nerves are the result of involvement of the respective nuclei and their nerves; the vertigo, nausea and vomiting and nystagmus are ascribed to lesions of the vestibular

nuclei and their connections with the nuclei of the vagus and oculomotor nerves; ipsilateral loss of pain and temperature sensation and corneal hypesthesia are caused by interruption of the spinal tract and nucleus of the trigeminal nerve, and the hypesthesia over the cheek is best explained by the involvement of some of the entering fibers of the trigeminal nerve. The absence of complete contralateral hypalgesia and thermohypesthesia is due to the extreme lateral and posterior position of the lesion, which spared most of the lateral spinothalamic tract. Horner's syndrome was related to the interruption of pupillodilator fibers, which are known to descend ipsilaterally from the hypothalamus and to converge in the lateral portion of the pons and medulla before continuing downward to connect with the sympathetic motor cells in the upper thoracic region.

Syndromes Resulting from Occlusion of the Cerebellar Arteries

Artery	Structures Supplied	Clinical Signs
Superior cerebellar	Brain stem Brachium conjunctivum Brachium pontis, upper portion Tegmentum of pons, lateral portion Cerebellum Anterior and posterior quadrangular lobules Superior semilunar lobule, anterior part Superior vermis Dentate, emboliform, globose and fastigial nuclei	Homolateral Cerebellar asynergia Involuntary choreiform movements Horner's syndrome Contralateral Loss of pain and temperature senses over face and body Sometimes partial deafness Sometimes weakness of face of central type
Anterior inferior cerebellar	Brain stem Brachium pontis, lower portion Restiform body Lateral tegmentum of upper part of medulla and lower portion of pons Cerebellum Flocculus Biventral lobules, lateral portion Superior and inferior semilunar lobules	Homolateral Cerebellar asynergia Horner's syndrome Deafness Complete paralysis of face Loss of pain and temperature senses over face Diminished light touch sense over face Contralateral Incomplete loss of pain and temperature senses over body
Posterior inferior cerebellar	Brain stem Restiform body Lateral tegmentum of medulla Cerebellum Biventral lobule, medial part Tonsil Inferior vermis Part of inferior semilunar lobule	Homolateral Cerebellar asynergia Horner's syndrome Loss of pain and temperature senses over face Dysphagia and dysphonia Contralateral Loss of pain and temperature senses over body

The signs of cerebellar ataxia cannot be assigned to a lesion of a single structure in the brain stem because, as is often the case in the other cerebellar artery syndromes, more than one cerebellar peduncle was involved, the inferior and the middle. Thus there was interference with both the spinocerebellar and the pontocerebellar system, to either of which the asynergia may have been due.

The same principles of diagnosis, so well known for the other vascular syndromes of the brain stem and cerebellum, seem to apply in cases of occlusion of the anterior inferior cerebellar artery. The onset of the disorder is usually sudden, with or without premonitory symptoms, and usually is unaccompanied by any loss of consciousness. Vertigo is the first and most important symptom and is often associated with nausea and vomiting. The other symptoms of facial paralysis, deafness, sensory disturbance and cerebellar asynergia appear in a few hours but may not all attract the attention of an unobservant patient. The diagnosis is at once obvious because of the association of signs of ipsilateral involvement of the cranial nerves and cerebellum. The clinical course is one of gradual improvement

over a variable period, and rarely is the condition fatal except as it provokes other complications, such as bronchopneumonia, or is part of extensive hypertensive vascular and renal disease. Notable by their absence are all signs pointing to involvement of the corticospinal tracts and medial lemnisci, which receive their blood supply from midline tributaries of the vertebral and basilar arteries.

As far as can be ascertained, the symptoms are related chiefly to softening of the lateral portions of the brain stem and cerebellar peduncles rather than to involvement of the cerebellar hemisphere. When an infarct is limited to the cerebellar hemisphere, vertigo may be the only clinical manifestation, or such a lesion may pass unnoticed and be unexpectedly discovered at autopsy.

The differential diagnosis of syndromes due to occlusion of the superior, the anterior inferior and the posterior inferior cerebellar artery is presented in the table.

Considering the variability of the arterial supply to the brain stem, it cannot be assumed with certainty that all syndromes caused by occlusion of the anterior inferior cerebellar artery will be identical with that in this case, but it is instructive to compare it with the syndromes in other cases. Unfortunately, Davison and Goodhart's case contributes little to knowledge of the syndrome because the arterial occlusion was incomplete and the softening limited to the cerebellum. It is to be noted that the cranial nerve signs distinguish between the anterior inferior and the posterior inferior cerebellar artery syndrome and that the extent of the sensory disturbance and the presence of homolateral choreiform movements characterize the superior cerebellar artery syndrome.

SUMMARY

The clinical and pathologic observations in a case of thrombosis of the anterior inferior cerebellar artery are presented. This syndrome is distinct from that which follows thrombosis of the posterior inferior and superior cerebellar arteries. Partial occlusion of the anterior inferior cerebellar artery is undoubtedly more common than has been believed, and it is expected that some of the distinctive features of this syndrome will permit their identification.

Neurological Unit, Boston City Hospital.

News and Comment

SCHOOL OF MILITARY NEUROPSYCHIATRY

The neuropsychiatric branch of the Surgeon General's Office announces the opening of the School of Military Neuropsychiatry at the Lawson General Hospital, Atlanta, Ga. The clinical and administrative practice of military neuropsychiatry presents many new and difficult problems to the newly commissioned neuropsychiatrist. The civilian professional experience of neuropsychiatrists varies considerably—i. e., psychoanalysis, neurology, state hospital psychiatry, prison psychiatry and child guidance—but on entering the Army they are faced with common problems, such as the selection and detection of mental misfits, the necessity for short periods of observation, puzzling and bizarre clinical manifestations peculiar to the military service and the administrative machinery set up to provide for the disposition of neuropsychiatric cases. It has been necessary, therefore, to provide some means whereby the practice of neuropsychiatry in the Army could be made more standard and uniform, to provide the individual officer with an opportunity to review subjects which he did not require in civilian life and to introduce him to the various administrative procedures which will bewilder him if no assistance is provided.

In recognition of these difficulties and to prepare the officer better for the handling of combat casualties, the School of Military Neuropsychiatry, which is unique in Army history and has already gained international attention, was developed, with the active interest and support of Major Gen. James C. Magee, the Surgeon General, and Brig. Gen. Charles C. Hillman, Chief of Professional Services, Office of the Surgeon General, to provide practical instruction for already trained and qualified specialists. Brig. Gen. William L. Sheep, Commanding General of Lawson General Hospital, a well known military neuropsychiatrist, is Commandant; the Assistant Commandant is Col. William C. Porter, also a prominent military neuropsychiatrist, who is in direct charge of the school. Colonel Porter teaches the military aspects of neuropsychiatry, on the basis of his broad experience. Dynamic psychiatry, from a military point of view, is taught by Lieut. Col. M. Ralph Kaufman, and psychiatry from an organic point of view is taught by Major Joseph L. Fetterman. Neurology is taught by Major William H. Everts. Lectures on other related subjects are given by specially selected officers, while certain members of the class relate special experiences, such as neuropsychiatry in the Air Corps, Tank Destroyer, Ranger and other special training camps. While these subjects are covered by some didactic lectures, much time is devoted to seminars and round table conferences. Clinical material of a type obtainable only in Army hospitals is provided, since experience has shown that the best method of teaching military neuropsychiatry is by constant reference to and the use of military casualties. In this manner the military administrative considerations which have presented, or may present, difficulties are thoroughly discussed. Thus the various aspects of military neuropsychiatry which confront the new officer and present difficulties to the older officers are well coordinated by excellent and experienced teachers. The advantages of mutual exchanges of experiences and opinions in the interest of uniformity and professional progress cannot be overestimated.

The quota of officers selected for each intensive four weeks' course, which began Jan. 2, 1943, includes officers from each service command and from the Air Corps, together with newly commissioned officers from training pools in general hospitals. In this manner, new officers have the advantage of the experience of older officers, and the older officers have, in turn, the opportunity of evaluating their experiences and methods in the light of experiences and methods of others. Here is demonstrated the adaptation of clinical teaching, the bedside method, to the field of military neuropsychiatry.

THE MEDICAL CORRECTIONAL ASSOCIATION

The Medical Correctional Association, an affiliate of the American Prison Association, is interested in establishing contact with all professional personnel who are specially concerned with or interested in the medical aspect of crime. Membership in this association is confined to the following groups:

(1) Physicians employed in penal and correctional institutions or jails; (2) physicians, social welfare workers and special workers who engage in medical research work in penal and correctional institutions or jails; (3) psychologists, physicians, social welfare workers and special workers engaged in medical research work in connection with (*a*) institutions or hospitals for the mentally ill, (*b*) mentally defective persons, (*c*) juvenile delinquents, (*d*)

defective delinquents, (*e*) outpatient or behavior clinics dealing with any aspect of crime or its prevention, (*f*) criminal, juvenile and domestic relations courts, (*g*) parole, (*h*) probation, (*i*) public and private schools, colleges and universities and (*j*) federal, state, county and municipal public health organizations; (4) any other person who, while not automatically falling in any one of the three aforementioned groups, presents satisfactory evidence that he or she is engaged in research or an occupation in which the medical aspects of crime are acknowledged as important features.

The annual dues of the association are $1, and their payment entitles the member to vote in the elections, to present papers before the open meeting of the association and to receive copies of the minutes, by-laws and abstracts of papers which have been presented at the annual meeting.

The present officers of the Medical Correctional Association are: president, Dr. J. D. Reichard, United States Public Health Service Hospital, Lexington, Ky.; first vice president, Dr. John W. Cronin, United States Public Health Service Hospital, Sheepshead Bay, N. Y.; second vice president, Dr. Lawrence Kolb, Assistant Surgeon General, Washington, D. C.; secretary-treasurer, Dr. Robert M. Lindner, Federal Penitentiary, Lewisburg, Pa.

Society Transactions

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

GEORGE A. BLAKESLEE, M.D.
President, New York Neurological Society, in the Chair

Joint Meeting, Oct. 6, 1942

Presidential Address: Neuropsychiatry in Wartime. DR. GEORGE A. BLAKESLEE.

This address was published in full in the December 1942 issue of the *Bulletin of the New York Academy of Medicine*, page 775.

Early Laminectomy for Injury of the Spinal Cord. DR. FOSTER KENNEDY, DR. PETER G. DENKER and (by invitation) DR. RAYMOND L. OSBORNE.

The controversy over whether laminectomy should be performed more frequently in cases of injury to the spinal cord is reviewed, and a study of the literature is presented. There has been a pendulum-like swing from conservatism to radicalism and back to conservatism again. At present most neurosurgeons seem to be excessively conservative in the treatment of this condition. Five illustrative cases in our experience at the Bellevue Hospital are presented. In all these cases severe injury to the cord had been sustained, and, because of the apparent hopelessness of the situation, the neurosurgeons were reluctant to operate. However, they were finally persuaded to perform laminectomy, since we felt that nothing was to be lost, and possibly something might be gained, by such a procedure. In all these cases definite lesions were encountered, which were helped by the surgical intervention. Scarring, fractures of laminas which did not appear in the roentgenogram, spicules of bone within the substance of the cord and other lesions were discovered when the cord was exposed; so it was felt that operation had really contributed a great deal to recovery in these cases. We therefore advocate more frequent laminectomy in cases of injury to the spinal cord, for the following reasons:

1. It is impossible to determine from neurologic examination at the time of the accident whether the cord has been completely severed or whether function has been physiologically interrupted.

2. Roentgenograms of the spine are by no means conclusive as to the presence of fracture of the laminas; on the other hand, spicules of bone may be pressing on the cord without appearing on the roentgenogram.

3. In the presence of manometric block, laminectomy should always be performed, regardless of whether it is felt that the injury to the cord is complete or not.

4. The operative mortality associated with laminectomy is so low that it should not be a factor in decision to operate. The operation is much less dangerous than is a diagnostic laparotomy.

5. No statistically followed series of cases has yet been reported in which treatment with laminectomy was employed in alternate cases. Such a study is advocated to decide the merits of this operation.

6. When operation is decided on, laminectomy should be performed early, since a case of injury to the spinal cord is a surgical emergency, and a delay of two to six weeks for "spinal shock" to subside is a needless waste of time.

This article was published in the April 1943 issue of the *American Journal of Surgery*.

DISCUSSION

DR. JOSEPH E. J. KING: There are probably two types of injury to the spinal cord for which one can decide to operate almost immediately, even without roentgenographic examination: first, a condition in which paraplegia has been produced by a direct blow on the back, directly over the spinous processes, such as a blow with a hammer, a fallen stone, a large shell

fragment, a piece of concrete, or a blackjack. The trauma to the cord, most likely, is due to crushing of the spinous processes and laminas, so that these bony structures impinge directly on the cord. It goes without saying that immediate operation is indicated. Second, gunshot wounds and stab wounds of the back producing paraplegia. In some cases of such injury rapid recovery may take place, but in many no improvement will occur, especially when the injury is produced by high velocity missiles. In a few cases observed during the first World War complete clinical division of the cord was produced by the rotary motion of such missiles, which merely went through the soft parts without touching the cord or even injuring the vertebral column. In other cases of gunshot and stab wounds the cord may be completely divided. Nevertheless, one is justified in making early exploration in the hope that only a lesser injury of the cord may be encountered.

The first laminectomy I ever witnessed was done by Dr. William A. Downes at the General Memorial Hospital in the summer of 1911. A well developed girl about 13 years of age had received a bullet wound in the back at about the level of the sixth dorsal segment. She was brought to the hospital completely paralyzed below that level. Dr. Downes observed that the .22 caliber bullet had passed through the dura in the midline and that the distal end of the bullet just protruded through the dura into the posterior longitudinal fissure, so that it had separated the posterior column, almost as though with a pair of blunt forceps. In February 1912 a photograph was received from the girl, in Canada, which showed her playing and throwing snowballs in the snow. She had completely recovered. Had the bullet not been removed, she might not have lived, and had operation not been done immediately, I think she would have been paraplegic, at least for a long time.

Most of the injuries to the spinal cord of the other type are associated with fracture or fracture-dislocation of the spine. As Dr. Kennedy stated in his paper, cases of fracture-dislocation in the cervical region are excluded, which leaves a rather large number involving the dorsal and lumbar regions of the spine. As Dr. Kennedy mentioned, neurosurgeons have been hesitant to perform early operation in cases of such injury—I believe for good reasons. Ordinarily the surgeon is ever ready to operate when he feels that any good will come of it. The reluctance to operate early is derived from experience of years, in which in a number of cases the cord has been found to be completely dissolved and the procedure useless. On the other hand, many patients have completely recovered, or improved to a considerable degree, without operation, provided the deformity was corrected.

I remember a patient whom Dr. Kennedy saw, a woman about 79 years of age. The automobile in which she was riding ran off the road and struck a tree, and she was thrown forward, receiving a horseshoe-shaped laceration of the scalp, which amounted to a partial avulsion. She had complete quadriplegia. She was brought to Lawrence Hospital, Bronxville, N. Y. One neurosurgeon wanted to operate, although roentgenograms showed no deformity of the cervical portion of the spine. The son of the patient, who was a surgeon, and Dr. Kennedy objected. No operation was performed. The patient was turned in bed, like a duck on a spit, and was catheterized by her son twice a day. After a while she began to move her arms, and finally the quadriplegia completely disappeared, with the exception of a slight residual paresis in the ulnar region of the left hand. I visited her in her home, and to all intents and purposes she had made a complete recovery.

Then in 1918, during the first World War, I saw a soldier who had been playing football; in making a flying tackle, which was allowed in those days, he was injured. The neurologists and surgeons did not think he should be operated on. There was no complete block. He recovered rather promptly and within three months was out of the hospital, walking about as well as ever. The level of his injury was about the eleventh dorsal segment.

These 2 cases represent what every neurosurgeon has seen, some rather frequently. On the other hand, all have seen instances in which the cord was completely divided, or if not, was so attenuated that it looked like two pencil points placed together, so that anatomic division had practically resulted. In view of these facts, the surgeons have shied away for the most part from immediate operation and prefer to effect correction of the deformity and wait, in most instances, for improvement.

A number of years ago Dr. Alfred S. Taylor and Dr. Claude Coleman told me that indication for immediate operation in a case of injury to the spinal cord depended, in their opinion, on the presence of complete block. I do not think that is right; nevertheless, it is what used to be taught. At times complete block may exist without destruction of the cord, and it is doubtful whether operation would be of benefit. On the other hand, it is possible that a spicule of bone may be driven into the cord, as Dr. Kennedy stated, without complete block. Therefore the rule of operation only for complete block does not hold.

Stereoscopic roentgenograms of the spine are not generally made, but there is no legitimate reason for not doing so. It is surprising how well one can visualize the component bony structures forming the wall of the spinal canal with such exposures, while in flat roentgenograms little detail can be seen. Really good roentgenologists, like Dr. Dyke and Dr. Law, would not think of reading roentgenograms of the skull unless they were stereoscopic, but for some reason most men are not accustomed to making stereoscopic roentgenograms of the spine. Stereoscopic roentgenograms of the spine show up just as clearly as do those of the skull. Therefore in all cases of injury, as well as other lesions, of the vertebral column with which I have anything to do I insist that good stereoscopic plates be made.

With regard to gunshot wounds in the first World War: In the neurologic services, and I do not know whether Dr. Stookey will bear me out or not, my associates and I encountered three main types of injury—those of the head, those of the spine and those of the peripheral nerves. We had a great many cases of injuries to the head, and an even greater number of injuries to the peripheral nerves, but few of injury to the spinal cord. Most of the men with such injuries died before they reached our hospital, and if they did not, quite a number died after arrival there. These deaths were due to ascending infection of the kidneys, or other infection, and a number of the patients gradually "faded out." As a whole, the group was a very poor one, and we had little success with them. Just what effect the sulfonamide drugs would have had in preventing the infections is not known. It is quite probable that more men with gunshot injuries of the spine in the present war will be operated on, with improvement, than in the last one.

Another point to be borne in mind can be illustrated by a case which I had not long ago at Bellevue Hospital. The patient, a young man, had a rather severe injury to his back, and paraplegia immediately developed. I saw him two or three weeks after his injury, at the hospital, and he had many severe bed sores. Lumbar puncture revealed complete block, and iodized poppyseed oil showed the obstruction. Laminectomy revealed a large central herniation of an intervertebral disk pressing against the cauda equina firmly, and to a severe degree. He made a complete recovery after removal of the disk.

One of the greatest additions to the methods of treatment of injuries of the spinal cord is Munro's tidal drainage. All are acquainted with the fact that in the past many patients with such injuries died not of injury to the cord per se but, rather, of ascending infection of the kidneys, from the bladder.

If an early operation is done, it should, and can, be performed readily with local anesthesia, especially since half the field is already anesthetic.

In conclusion, I wish to say that we surgeons are willing to operate in certain cases early, or immediately, provided the neurologists can show definite reasons for doing so. We are not lazy, and we are glad to do the work when we are convinced that better results would thus be obtained. I feel sure that in some cases immediate operation should be performed, that in many cases no operation is required and that in others, even if operation is carried out, little improvement will result.

DR. BYRON STOOKEY: Dr. Kennedy cited Sir Charles Bell; as I recall, Bell advised against operation. He objected to one's comparing the removal of a piece of bone which is pressing on the brain with the same procedure in relation to the spinal cord. He called attention to the fact that a piece of bone presses only on a small amount of the total substance of the brain, while as a rule it presses on the total substance of the spinal cord.

Dr. Kennedy stressed the brilliant experiments of Allen, which raises a point of especial interest in the present discussion. There is in the dog no extra room within the vertebral canal or around the dura, such as exists in man. In man there is a large factor of safety in the relative sizes of the spinal cord, the dural sac and the vertebral canal, so that the spinal cord in many parts of the vertebral canal can swell to almost twice its normal size and still not be impinged on by the surrounding structures. Allen's recommendation of making multiple incisions in the dorsal portion of the cord I should consider of doubtful application to man because of the difficulties involved, the bleeding that would attend it and the disruption of part of the function of the dorsal column that would result. However, if by so doing the major portion of the function of the spinal cord could be regained, I should think it worth the doing.

The problem is not that the surgeon is afraid or unwilling to operate or that the operation is difficult; rather the question is whether he can improve the patient's condition. I agree thoroughly with the recommendations by Dr. Kennedy and Dr. King with regard to gunshot wounds of the spinal cord, for which much more can be offered by exploration than by waiting. The wound can be cleaned out and *nettoyage* of the field done, and perhaps foreign bodies can be removed and the cord given whatever chance it may have to recover. Most neurosurgeons would be inclined to operate under such conditions, the operation, of course,

being preceded by stereoscopic roentgenographic study, as Dr. King indicated. On the other hand, if the bullet tract is filled with minute spicules of bone that can be seen within the vertebral canal, operation might be inadvisable.

Dr. Kennedy cited the case in which Dr. Stetten operated. I remember his reporting that case before the New York Surgical Society some years ago, and I think all are agreed on operating in such cases. If I recall correctly, the man was hit on the back of the neck by a blackjack, with fracture of the arches of certain cervical vertebrae. Stereoscopic roentgenograms would have shown this had they been taken. I think one is justified in operating in cases of injury to the cord from a direct blow. Neurosurgeons are in accord as to the advisability of exploration in such cases, but they are relatively rare in civilian life, especially those of injury from gunshot wounds. The majority of cases are those in which a deformity has been produced by jackknifing and compression. By operation the surgeon can only relieve the pressure on the cord; he can do nothing more for the damage to the cord except clean up the wound. By removal of the arches he still leaves severe angulation of the bodies of the vertebrae, and the angulation of the bodies is often more damaging to the remnants of the spinal cord than operative removal of the pressure. The principle of treatment is to remove the pressure on the cord, and more recent advances in the methods of reduction offer the patient more than operation can, for if the reduction is well done, it not only reduces the pressure on the dorsal aspect of the cord but removes the compression of the ventral aspect, which is much sharper and of greater significance. With Crutchfield's tongs, attached in a small hole in the outer table of the skull, traction can be applied in a few minutes, and reduction accomplished without operation. When the pressure that is causing the difficulty can be removed by skeletal traction and reduction without operation, there is the possibility that a stable vertebral column will be established. When the arches are taken off, and the laminectomy must, of necessity, involve a minimum of three vertebrae in order to accomplish any reduction of pressure, one has removed certain factors making for stability of that portion of the spine. Because the surgeon feels he can do nothing to improve the patient's condition except remove pressure, he prefers to remove that pressure by skeletal traction and other methods of reduction. By these means I have been able to reduce decided deformities of the spine, and hence I think the nonoperative approach is the more desirable.

The manometric test indicates only an obstruction. That obstruction may be mechanical, due to displaced vertebral fragments, or it may be caused by edema. Edema cannot be relieved by the surgeon. He can only make more room by opening the dura, and thus relieve the pressure caused by the edema. With the modern use of hypertonic solutions, which formerly were not available, but which I think should be used in cases of acute injury to the spinal cord, and have been so employed in Dr. Scarff's service at Bellevue Hospital, this edema can be relieved. Therefore the presence of edema is not, I believe, a valid indication for operation. No one here can be a more enthusiastic supporter of the manometric test in diagnostic procedures related to the spinal cord than I am, but for edema it is of doubtful value, for while it does indicate a block, that block may be due to edema, which can be relieved conservatively by use of hypertonic solutions. We surgeons have a great deal of respect for the spinal cord and the ease with which it is damaged, and, when damaged, the ease with which any remaining function may be further jeopardized; hence our conservative attitude has a great deal to commend it in certain cases at least.

I had an opportunity to review the 5 cases which Dr. Kennedy has cited here. In the first case there was probably a unilateral dislocation. An operation was performed; perhaps Dr. Kennedy or Dr. Denker can tell whether any attempt was made to reduce the offending dislocated vertebra. Certainly, that should have been done first. I have had to operate in cases of unilateral dislocation because I could not get a reduction otherwise. Even then, in 2 cases I was not able to obtain a reduction by placing a lever underneath the arch, and I had to open the lamina in order to relieve pressure on the cord.

Dr. Peter G. Denker: I do not believe any attempt was made to reduce the fracture first.

Dr. Byron Stookey: I think it should have been done. In 1 of the other cases the injury was a gunshot wound, and I should certainly have operated in this case. Another case cited was that of Dr. Stetten in which the man was struck over the back of the neck with a blackjack and had a fracture of a posterior arch. In that case I believe an operation should have been done. In 1 of the other cases a pregnant woman tripped and fell forward on the floor; she got up and was able to walk; a week later she noted numbness of the legs, and subsequently there developed a sensory level from the twelfth to the tenth thoracic. She was operated on, although roentgenogram did not show any dislocation. I do not believe Dr. Kennedy saw this patient, and I wonder whether there was actually an injury to the cord. I have never known of any patient falling forward and damaging the spinal cord. It has

always been a jack knife fall that has done it. I wonder whether the case could have been one of myelitis or infection.

DR. PETER G. DENKER: The woman had complete block on two successive days.

DR. BYRON STOOKEY: I appreciate that. I shall never forget an operation which I performed with Dr. Taylor on a woman in whom transverse myelitis developed overnight. She had a large, swollen cord. Dr. Kennedy and his associates will have to demonstrate the injury to the cord in this case; I do not believe it is substantiated in the report. In the other case there were multiple displacements, apparently involving several lumbar vertebrae; at operation, and wisely I believe, the dura was not opened. It is wise sometimes not to open the dura, for, in my experience, when the dura is opened the damaged cord may ooze out, so that, as Dr. King said, whatever chance the patient has, and probably there is none, is taken away.

Dr. Taylor has been cited here as one who advises operation. From my experience with him in the last ten years of his practice I know he did not recommend surgical intervention, for he had evolved one of the best methods of closed reduction which was available at that time. He advised me strongly against operative procedures. We saw a patient at the Beekman St. Hospital, and I did the operation. I did not reduce the fracture but, rather, did a decompression and I kept the patient under observation until he died, about fifteen years later. He had pronounced wedging, in which the anterior surface of the wedge was 4 to 5 mm. in thickness, a severe deformity, and whatever chance the man may have had I must have taken away from him. So, in summary, I do not believe that in these 5 cases Dr. Kennedy has presented enough evidence to warrant a change in opinion on the part of any surgeon who disagrees with him. I agree that gunshot wounds, at least in the early stage, should be explored after study unless there is some contraindication, and that the wounds resulting from direct blows, with fracture of the posterior arches, should likewise be explored, but I question seriously the value of attempting to remove pressure from the cord by operation, which is all the surgeon can do, when the real deformity is in the body of the vertebra. I believe the operation only weakens the vertebral column.

DR. FOSTER KENNEDY: I rather thought I had forestalled this argument by saying at the beginning that dislocations did not come into consideration here.

DR. BYRON STOOKEY: Subluxations are different from real dislocations.

DR. FOSTER KENNEDY: Of course I mean subluxations—one can hardly reduce a dislocation. With a subluxation of the vertebral column one ought to try to make a closed reduction. The case of the elderly woman that Dr. King spoke of is a perfect example. She was treated with prolonged hyperextension, and although she had been paraplegic at the beginning, she had at the end, as Dr. King said, slight involvement of only one hand. When I went in to see her she was on a high catafalque in a great room. Her son had told me what a good patient she had been. I approached the catafalque cautiously in the gloom and said to her, just to break the ice: "Mrs. X, I hear you are a very good patient." She was totally paralyzed and could not turn her head, which was in hyperextension; so she turned her eyes sharply to the right and looked at me and said: "Dr. Kennedy, when one is 80 years old, and paralyzed in all four limbs, there is nothing left for one but virtue." A person like that could scarcely help getting well.

Sir Charles Bell's ghost was evoked in our paper merely to give it respectability by historical reference. His opinions, however fine his mind was, can hardly be of great value now, in view of the neurosurgery of his day. I do not feel that neurosurgeons have a sufficient regard for themselves. They view themselves in a diminishing mirror, so that they seem to themselves—or is it to each other?—too small. We physicians think them potent and important and feel they should go about their business a little more urgently. Dr. Stookey will, I am sure, subscribe to the idea that the urging on the part of the physician to explore the known level of spinal disease has revealed a great many pathologic, and often curable, situations. That is exactly my point in this argument: the surgeon cannot tell beforehand what he may find. If he knows he is dealing with a subluxation or a dislocation, it is his duty to reduce it if possible, but if he does not know what the situation is, it is his duty to explore. He does not know what the situation is until he has looked. Another thing, Dr. Stookey's criterion for operation is: "What can be done to improve the condition?" One cannot tell what one can do to improve the condition until one explores. A pontifical statement that the cord is smashed beyond repair may be wrong. I know instances, such as those cited in this paper, in which I believed the patient would not have recovered had exploration not been done. Then, too, the patient must be considered. I remember a young physician who had, I believe, a completely smashed cord. I had advised operation at the time of the injury. A surgeon had advised against it, and the man was not operated on. He remained paraplegic

and very ill for a year; he was extremely unhappy and disturbed because he felt that no one knew the state of his spinal cord for certain. At the end of about a year, I advised the physician to submit to operation on the spine, although I did not believe that any benefit would result, as there did not. The cord was pulped at the level of the lesion, but after operation and the securing of certainty the patient completely changed as a human organism. His adaptation to his incurable condition became perfect almost overnight; he knew exactly where he was. Such is the value of certainty and decision in giving peace and power with which one may deal with a lamentable situation. I told the patient before the operation that I looked on the laminectomy as a psychologic treatment, that I did not think it would do him any physical good, but it might help his emotional adjustment.

Effect of Vitamin E Therapy on the Central Nervous System in Amyotrophic Lateral Sclerosis. DR. CHARLES DAVISON.

In 10 cases of amyotrophic lateral sclerosis treatment was instituted with vitamin E and alpha tocopherol, and, except in 1 instance, there was no clinical response to this therapy.

Histologically, however, in 6 of the cases in which intensive treatment had been carried out destruction of the myelin sheaths and axis-cylinders was much less severe than in the cases in which no treatment was given. The dense gliosis which is usually present in amyotrophic lateral sclerosis was diminished, or almost absent, in the cases in which vitamin E was administered. The lessened destruction of myelin sheaths and axis-cylinders and the faint gliosis in these instances were perivascular and insular. In 1 of these cases the beneficial changes were limited to one side of the cord only. The nerve cells of the involved bulbar nuclei and the anterior horns remained unchanged and showed no signs of reversibility.

The histopathologic process in the other 4 cases, in which treatment was less intensive, was concluded to be similar, although less extensive, to that in cases in which no treatment was given.

There is a possibility that vitamin E therapy in cases of amyotrophic lateral sclerosis resulted in a reversal of the degenerative reaction, affecting simultaneously and equally the myelin sheaths, the axis-cylinders and the glia.

DISCUSSION

DR. TRACY PUTNAM: This is an interesting approach to the subject of amyotrophic lateral sclerosis, and Dr. Davison's beautiful preparations speak for themselves. On the basis of my own experience I feel he is unquestionably right that there is a stage of myelin degeneration which is reversible. This can be clearly shown in animals. If one induces demyelination of axis-cylinders in one area, which can be done in any one of several ways, and follows the animals for a time, killing them at intervals, it is quite clear there is a reversible stage of damage to the myelin, and then an irreversible stage. In no animal I have seen, and I think Dr. Ferraro has had the same experience, has there been any return of myelin after complete removal from the axis-cylinders, even after periods as long as fifteen months. If this does not happen in animals, I am skeptical about its occurring in human beings. All agree with Dr. Davison that when the axis-cylinder is actually interrupted regeneration cannot be expected, but when the axis-cylinder is continuous, and merely swollen or tortuous, the process may be reversible.

Dr. Davison has presented some new data which deserve to be closely scrutinized, but they are perhaps open to another interpretation. In a recent survey of all the cases of amyotrophic lateral sclerosis in the records of the Neurological Institute, Dr. Roy Swank and I found that the picture was extremely variable, and that there was every gradation between the classic Charcot type, with atrophy of the hands and spasticity in the legs, and spinal muscular atrophy, on one end of the scale, and, on the other, the rather rarer type of lateral sclerosis. In cases in which no treatment had been given, we found that the prognosis was far worse for the classic form, with well pronounced signs of involvement of the pyramidal tract. The prognosis was much better if the disease was atypical, and as all know, for the pure lateral sclerosis or the pure muscular atrophy the prognosis was not poor.

The notes show that in the 6 cases in which less than average demyelination was present, the signs referable to the pyramidal tract, even before treatment was started, were rather insignificant. There was a negative Babinski sign in cases 1, 2 and 3; in case 4 there was a positive Babinski sign; in case 5 the signs referable to the pyramidal tract were relatively mild, and in case 6 they were not extreme. In 3 of the cases the symptoms were chiefly bulbar, and the patients died of pneumonia. It seems quite possible that in these cases more amyotrophy and less defect in the pyramidal tract were present from the beginning, and that is perhaps why fewer changes were evident in the lateral column. Dr. Davison's analysis has

shown that all the changes are associated, and this is a rather general rule in neuropathology. If there is degeneration of myelin there is gliosis also, unless some nutritional lack prevents it. The fact that no loss of myelin and no gliosis was noted in these cases suggests there had never been loss of myelin to the extent seen in the other cases. I note that in the second group of 4 cases there were, even before treatment, evidences of serious defects in the pyramidal tracts and, in proportion, rather fewer bulbar symptoms. I should like, therefore, to ask Dr. Davison whether it is possible that from the beginning the first group of cases differed from the average, or classic, case.

DR. ISRAEL WECHSLER: Like Dr. Putnam, I do not know just what to make of the slides which Dr. Davison showed. It is difficult to draw conclusions concerning recovery from microscopic sections taken at autopsy. I saw the slides for the first time tonight, and it has all come as a surprise. Evidently, Dr. Davison has demonstrated less degeneration in treated than in untreated patients.

From a clinical point of view it is clear that the vast majority of patients do not respond to treatment. I shall soon have complete records on 70 patients, about 60 of whom showed no improvement; the rest did. Several of them, some of whom I presented at a meeting of this society two years ago (Amyotrophic Lateral Sclerosis Treated with Synthetic Vitamin E, ARCH. NEUROL. & PSYCHIAT. **45**:873 [May] 1941), are still living. They are not very good specimens of health, but they are alive. It is my opinion that amyotrophic lateral sclerosis is not one disease, but a series of syndromes. There is an inflammatory type, as Wimmer showed long ago. In a great many cases the disease has a vascular origin. A small number of cases may belong to the group of deficiencies. It is known that vitamin deficiency causes "degenerative" changes, and since the pathologic process in amyotrophic lateral sclerosis resembles that seen in avitaminosis the inference may be justified that deficiency also plays a part in some cases at least. Whether this is true I do not know, nor am I certain that one is dealing with a vitamin E deficiency in my cases. There is some evidence that an X factor operates in some cases.

My associates and I are still working with patients despite the discouraging results of the past two years. We know, for instance, that hypodermic injection of tocopherol is no better than, and perhaps not as good as, oral administration. With a test perfected by Drs. Sobotka and Mayer the uptake of tocopherol in the blood can be measured. It seems that the blood curve does not rise with doses over 100 mg., no matter how much is administered.

My own interest in the question of degenerative processes in general is even greater than in amyotrophic lateral sclerosis itself. All know how unsatisfactory the word degeneration is—that it is an autopsy diagnosis in vivo. What one means by it is disappearance of nerve cells, myelin and axis-cylinders, and replacement with glia tissue in some cases. The underlying dynamics of the production of degenerative processes is not understood. Whether the slides shown here contribute to one's knowledge, whether they point to less "degeneration" or to a difference in reparative processes is a matter of opinion.

It seems to me that characteristic of amyotrophic lateral sclerosis is a discrepancy between the functional, or neurologic, picture and the anatomic substratum. One may observe severe degeneration of the pyramidal tracts on section and record few signs during life. It is known how frequently a Babinski sign is lacking and the abdominal reflexes are present despite tremendous involvement of the pyramidal tracts. In a measure, this is true of the discrepancy between functional and structural impairment in multiple sclerosis. One often observes a white optic disk which should cause total blindness, and yet the patient has fair vision. The usual explanation is that the preservation of the axis-cylinder permits function to continue, but that is not always true.

In conclusion, I should like to feel happy about Dr. Davison's demonstration, and I hope that what he said is valid. I can only repeat that I think a small proportion of cases of amyotrophic lateral sclerosis belong to the vitamin deficiency group, but that remains to be proved.

DR. A. M. RABINER: This presentation by Dr. Davison adds to the perplexity that began when I listened to Dr. Wechsler's original paper two years ago. At that time I questioned the basis for the therapy recommended because the rats which had been studied for sterility had, as a result of vitamin E deficiency, shown muscular atrophy and weakness. This was supposedly due to disease of the pyramidal tract. My perplexity arose from the fact that there is considerable doubt whether the rat has a tract that can be called the pyramidal tract. There are some fibers in the rat's spinal cord that have been so labeled. It is questionable whether this is correct for animals that are predominantly quadruped. The horse and sheep have few pyramidal fibers demonstrable in the brain after excision of the motor cortex and no pyramidal tract fibers demonstrable below the cervical level in the cord. Because of this, I thought it

more likely that therapeutic improvement in cases of amyotrophic lateral sclerosis was ascribable to the influence on the anterior horn cells than on the pyramidal tracts. Some of my associates, later, after having given a number of patients vitamin E, concluded that some of the fibrillations disappeared and the patients themselves seemed subjectively better. Now Dr. Davison presents pathologic material demonstrating no changes whatever in the anterior horn cells after vitamin E therapy, but some possible improvement in the appearance of the pyramidal tract.

DR. CHARLES DAVISON: Like Dr. Putnam, I have in a previous paper (Amyotrophic Lateral Sclerosis: Origin and Extent of the Upper Motor Neuron Lesion, ARCH. NEUROL. & PSYCHIAT. **46**:1039 [Dec.] 1941) emphasized the pathologic and etiologic variability in cases of amyotrophic lateral sclerosis. In this, and in other papers, I showed that the demyelination in a number of cases of amyotrophic lateral sclerosis is not limited to the pyramidal tract but may extend to the other ventrolateral tracts or to the posterior column. Since this communication I have reviewed 36 other cases of the disease in which necropsy was performed, cases studied clinically by competent observers and recognized as true instances of amyotrophic lateral sclerosis, and have found only 2 in which the demyelination could not be seen in the gross myelin sheath preparations. One of these 2 cases, because of mental symptoms and some extrapyramidal features, was considered an instance of spastic pseudosclerosis.

In reviewing the 6 cases, as Dr. Putnam did, it should be emphasized that absence of the Babinski sign in amyotrophic lateral sclerosis does not mean absence of a lesion of the pyramidal tract. In this illness there is disease of the anterior horn cells and of the pyramidal tract. In many cases of amyotrophic lateral sclerosis, because of the disease of the anterior horn cells, reflexes may not be exaggerated or pathologic. Exaggeration or intactness of reflexes in the presence of disease of the anterior horn cells signifies only one thing, disease of the pyramidal tract.

In cases of progressive spinal muscular atrophy, purely a disease of the anterior horn cells, the reflexes cannot be elicited at all, for here pyramidal degeneration cannot be demonstrated.

DR. HENRY A. RILEY: Did the patients have any weakness?

DR. CHARLES DAVISON: Yes, all the patients had weakness, atrophy and fibrillations.

In cases 1, 2, 3, 5 and 6 hyperactive reflexes and diminished abdominal reflexes were noted. There were a positive Babinski sign in the fourth case and a bilateral Hoffmann sign in the sixth. Of the 4 so-called control cases, no Babinski sign was elicited in the ninth and tenth. I believe that the changes in these 6 cases should not be interpreted as pathologic variations of amyotrophic lateral sclerosis. Why should they have occurred in succession and in such large numbers just when the treatment was given? It could not be a mere coincidence. The lack of gliosis, I agree with Dr. Putnam, is difficult to explain, but it is what I saw.

PHILADELPHIA NEUROLOGICAL SOCIETY

F. H. LEWEY, M.D., *Presiding*

Regular Meeting, Oct. 23, 1942

Primacy of Area 13 of the Orbital Surface of the Cerebral Cortex in the Production of Hyperactivity in Monkeys. DR. HENRY A. SHENKIN and DR. THEODORE C. RUCH.

Bilateral ablation of the posterior orbital gyrus, which Walker recently differentiated as a new cytoarchitectural area (area 13) and which Bailey, Baemer and Sweet demarcated physiologically from adjoining areas, was performed in a series of monkeys. This procedure produces in a notable degree many of the symptoms that have been described for prefrontal lobectomy by various workers. They are as follows:

1. Hyperactivity is manifested by long-continued, methodic pacing or running of a regular, stereotyped character.

2. Hyperactivity from lesions in area 13 is quantitatively great, is consistently obtained and is always manifested in some degree within even the first or the second postoperative day, whereas similar hyperactivity from other prefrontal areas is said to be delayed in onset (as long as two to three weeks) and does not invariably occur. For these reasons it is concluded that area 13 is a focal representation which controls the activity level of the monkey.

3. Other motor activities are not marked by hyperactivity, but rather suffer reduction. Random, spontaneous activities and posturings are reduced in variety and in quantity, as is emotional expressiveness. There are also certain ill defined behavior changes. All of these symptoms are most evident in the first postoperative week.

4. Hyperactivity is accompanied by loss in weight and a slight increase in food intake.

DISCUSSION

DR. SARAH S. TOWER, Baltimore: This paper is interesting to me because it explains why I have been failing for some years to obtain, with electrical stimulation of the frontal lobe of the monkey, a type of response which is so readily and strikingly obtained in the cat, that is, arrest of spontaneous movement.

There is, of course, an enormous difference between the cat's and the monkey's prefrontal lobe. The cat has almost none, and what it has is cytoarchitecturally undeveloped. All of it is fairly readily accessible and I have stimulated the whole, but in the monkey I never have stimulated the orbital surface. I have been able to stimulate only the dorsal and lateral surfaces of the frontal pole, either by exposure or with implanted electrodes. Under these circumstances, I have rarely been able to demonstrate in the monkey a result which is most striking in the cat, inhibition of spontaneous activity.

In these experiments with the cat, the frontal pole is exposed with the animal resting on a stand and under very light ether anesthesia. Under these circumstances, there may develop spontaneous rhythmic wagging movements of the tail, chewing movements of the jaw, running movements involving all four extremities, nystagmoid movements of the eyes or other rhythmic movements, which one can count on to be continued for minutes, or perhaps indefinitely. Stimulation of the frontal pole, then, depending on the strength of the stimulus, will slow such movement or arrest it, and hold it in arrest, until stimulation is discontinued. Thereafter, the movement will resume, often with a poststimulatory escape, like a rebound phenomenon.

In the monkey I had expected, because of Dr. Richter's and Dr. Hine's previous results with bilateral frontal lobectomy, to find a similar electrically excitable effect, but there was none. There is another inhibitory action against spontaneous movement, both in the monkey and in the cat: a quieting effect, which is generally distributed. But I could never find in the monkey's cortex the powerful arresting effect so conspicuous in the cat. However, I never stimulated the orbital surface of the frontal lobe, because of technical difficulties.

I should like to ask the authors what they know of the cytoarchitecture of area 13. Is it a developed type of cortex, or is it primitive, like the whole prefrontal lobe in the cat?

DR. H. A. SHENKIN: As I understand it, it is a primitive cortex, not at all developed. It is merely a small subdivision of the general prefrontal cytoarchitecture.

DR. SARAH S. TOWER, Baltimore: What is the ratio of the supragranular to the infragranular layer? In the cat the whole prefrontal area has a poorly developed supragranular layer.

DR. H. A. SHENKIN: To be frank, I am not sure what the ratio is for this area. That the area is really well delineated is supported by the fact that Bailey and Sweet have rcorded specific stimulatory effects from this region.

DR. SARAH S. TOWER, Baltimore: It is from this area that they got the changes in respiration, is it not? The whole prefrontal lobe of the cat, which appears to be a unit, can slow or arrest respiration.

DR. H. A. SHENKIN: Bailey and Sweet found the effects on respiration to be particularly limited to this cytoarchitectural area, and this is physiologic evidence for the validity of the differentiation.

DR. SARAH S. TOWER, Baltimore: I wonder if one can consider area 13 in the monkey the homologue of the carnivore's entire prefrontal lobe, and all the other areas—9, 10, 11, 12 and the 40's, all highly developed cytoarchiecturally as something added.

DR. H. A. SHENKIN: As I recall, area 13 is just as well developed as any of the surrounding areas. These areas are certainly not as primitive as the prefrontal cortex of the cat, but in relation to other regions of the monkey brain area 13 is not a developed cortex. However, specific localization to this area in the monkey is certainly conceivable.

DR. SARAH S. TOWER, Baltimore: Not much is known of the phylogenetic development of this region, is there?

DR. H. A. SHENKIN: I don't know much about it, anyway.

DR. B. J. ALPERS: I should like to ask Dr. Shenkin whether, with destruction of area 13, there is any change in the emotional reactions of his monkeys I ask this because of the association in the minds of some persons between lesions of the frontal lobe and loss of aggres-

sive tendencies. I wonder, also, whether the overactivity which he describes is pure overactivity, of whether it represents loss of inhibition or a personality change on the part of the monkey which is expressed in overactivity.

DR. H. A. SHENKIN: We did not ablate areas other than 13 in these animals. However, it is not an uncommon experience of other workers who have ablated the entire prefrontal lobe to observe diminution of activity in the first few weeks, followed by hyperactivity.

Such an effect makes one wonder, perhaps, if there had not been ablated in addition an excitatory area, which resulted in inhibition of activity—for example, area 8, which Dr. Kennard has ablated in many animals. Her animals sit with their heads between their shoulders and will not indulge in any voluntary activity; this inactivity is followed, if further removal of the prefrontal lobe is carried out, by hyperactivity. There was no change in respiratory rate that we could notice. Oxygen consumption was not altered from that before operation.

Fulton and Watts (*Ann. Surg.* **101**:363 [Jan.] 1935) reported cases of intussusception in animals with prefrontal ablations. In our experiments, in which we measured the time required for carmine to pass in the feces, we could demonstrate no change in gastrointestinal motility. Accurate measurement revealed a slight increase in food intake, which could be accounted for by the increase of activity rather than by any metabolic alteration. We could detect no metabolic changes in our animals.

DR. SARAH S. TOWER, Baltimore: I wish to ask the authors whether their monkeys showed absence of the threat reaction when a pass was made before their eyes. The bilateral frontal lobectomy preparations of Dr. Hines, which I have had under observation for several years, are not as appreciative of threatening situations as is an ordinary monkey, to the extent that one must be careful with what other monkeys they are placed.

DR. H. A. SHENKIN: Exactly.

DR. B. J. ALPERS: I am interested in the personality changes in general. It is a little difficult to conceive of overactivity as overactivity without some accompanying process.

DR. F. H. LEWEY: In the literature the term "overactivity" is not used in the sense of "hypermotility" in this connection. The word refers exclusively to pacing and does not contain any inference as to the cause of pacing.

DR. H. A. SHENKIN: I think that this interpretation of the term is right.

DR. B. J. ALPERS: This state of overactivity is more than pacing, it is a spread of activity, as I understand it. There is a great deal of activity.

DR. H. A. SHENKIN: All the animals do is pace. There is a personality deficit; they do not react to the presence of visitors as do other monkeys. They show no fear. One can approach them closely before they make any sign of recognition. In the first few weeks they sit gazing off into the distance and pay no attention to anything you may be doing; this is unusual for a monkey, who always has his eyes on you, in one way or another.

Later, instead of reacting in an aggressive fashion, they simply increase the rate of their pacing. The record shows this to occur without the interruption of side actions. They just keep going.

DR. SARAH S. TOWER, Baltimore: Is the region in the human brain corresponding to area 13 ever ablated in removal of the frontal lobe?

DR. H. A. SHENKIN: I doubt it. In man this area would be far back toward the olfactory striae. I doubt whether lobectomy would extend that far.

Dr. F. H. LEWEY: One of the interesting points in this presentation is that only bilateral, not unilateral, frontal lobectomy produces pacing. Is there any notable difference in the behavior of persons after unilateral and after bilateral frontal lobectomy for tumor of the brain?

DR. G. D. GAMMON: These reactions were described as pacing reactions; they seem to me to be due partly to the monkey's being confined in a cage. What happens to him if he is turned loose?

DR. H. A. SHENKIN: We have not willingly turned the animals loose. They have escaped on occasion. They will follow the perimeter of the particular confining space that they are in. However, one monkey had a habit of performing a figure eight; only, when he escaped it was a large, instead of a small, figure eight.

Pyramidal and Extrapyramidal Mechanisms in the Cortical Control of Movement.
DR. SARAH S. TOWER, Baltimore.

The cerebral motor cortex has at its command one avenue for direct action on the final motor mechanism, the pyramidal tract, and an indeterminate number of indirect avenues, called in the aggregate the extrapyramidal systems. When the medullary pyramid is severed, the

pyramidal tract alone is interrupted, the extrapyramidal systems being left intact. The functions of the pyramidal tract may then be inferred from the symptoms produced by the lesion, while the functions of the extrapyramidal systems may be studied either in the performance of the intact animal or by electrical stimulation of the cerebral cortex. Studies of this design were carried out on cats, monkeys and chimpanzees and in cases of similar lesions in man collected from the literature. The outstanding results are as follows:

The pyramidal tract has both phasic and tonic functions. Discrete control of movement is the main phasic function. The tonic function reenforces tone and reflexes. A lesion of the pyramidal tract produces characteristically hypertonic paresis, attended in apes and man by the sign of Babinski.

The cortical extrapyramidal systems function both to initiate stereotyped movements or acts and to inhibit tone and movement of skeletal muscles. These various functions are exercised from separate, though overlapping, cortical fields.

Pyramidal and extrapyramidal functions are completely integrated in the totality of cortical motor function.

DISCUSSION

DR. G. P. MCCOUCH: Before discussing Dr. Tower's paper, I wish to express the enthusiasm all feel in the presence of a master in her field who has done a piece of work so thoroughly that no room is left for after-thoughts as to the need of confirmation.

I shall restrict my remarks to the final stage of motor integration. Dr. Tower has spoken of the pyramidal tract as essentially motor, its inhibitory effect being limited to muscles antagonistic to the movement induced. This is precisely the distribution of inhibition that characterizes reflexes of movement. Like the reflex afferent fibers, the corticospinal fibers are now known to terminate dominantly on interneurons, and not, as pictured in the textbooks, on motoneurons. The temptation is strong to assume that reciprocal innervation is mediated solely by the interneurons of the cord and that the corticospinal neurons are purely excitatory. Thus, the entire process could be blocked most readily at the internuncial level. In the case of the flexor response it is precisely at this level that the major share of inhibition by a preceding conditioning stimulus falls.

Of the changes in reflexes, the most radical and puzzling is the Babinski response. I like to think of it as the reversion of function of a two joint muscle, the extensor hallucis longus, from a digital response, under pyramidal control, to flexion of the ankle, under the drive of a spinal reflex.

I fear I am yielding to the temptation to digress into speculation, which Dr. Tower has so meticulously avoided. My excuse is that the primrose path was painted by a penetrating suggestion in one of her own papers.

DR. SARAH S. TOWER: The pyramidal system operates entirely within, one might say, the functional organization of the segmental level. Hence discrete movement and reciprocal inhibition go hand in hand, just as Hering and Sherrington said long ago. But in the cat's motor area, and less conspicuously in the monkey's, after the pyramidal system is cut there is still a tonic inhibitory mechanism, the extrapyramidal, which can be brought into play, and without any following motor act; in this respect it differs from pyramidal inhibition, which can never be dissociated from its corresponding excitation.

DR. G. P. MCCOUCH: In this regard pyramidal inhibition is somewhat analogous to the reflex situation, in that one cannot dissociate the movement from the inhibition.

DR. SARAH S. TOWER: I should put it in this way: The segmental motor mechanism cannot be made to operate other than under its own laws.

DR. G. P. MCCOUCH: So, Dr. Tower, you regard the reciprocal inhibition as essentially spinal?

DR. SARAH S. TOWER: Yes. With respect to the Babinski sign, in the chimpanzee it is outstandingly a mass response. It is difficult to elicit a Babinski response in the chimpanzee without cocontraction of the flexor muscles of the thigh, and sometimes of the long adductor muscles.

I have puzzled a great deal about what really goes into the making of a Babinski response, and I am not sure that I know. There is a great deal of difference between the organization of muscles in the chimpanzee and that in the human being. Dr. McCouch's suggestion perhaps best accounts for it.

There are shifts in emphasis. The effect of pyramidal lesion differs quantitatively with different muscle groups—it is graver for some muscles than for others; that is, the balance of tonic innervation is quite different after pyramidal lesion than it is in the intact animal.

A pyramidal lesion modifies the pattern of excitability of reflexes to a considerable degree; it is not the same in the chimpanzee as it is in the monkey, and it is not the same in the monkey

as it is in the cat. The pyramidal system in the cat operates mostly on the flexor muscles. In the monkey its action is pretty well balanced between the flexor and the extensor groups. In the chimpanzee its influence is on the other side; the extensors, I think, get a little more of it.

DR. G. P. MCCOUCH: Incidentally, is it Dr. Tower's experience that with a sufficiently large ablation one may get the equivalent of a Babinski response in the monkey? The only monkey in which I have seen such an effect was a hemidecerebrate preparation of Fulton's, which showed not a Babinski, but a Chaddock, sign, perhaps the equivalent.

DR. SARAH S. TOWER, Baltimore: I have seen the Babinski response in monkeys, but it is not a reliable sign. There seem to be individual factors in it, actually. In some monkeys the toes turn up and in some they turn down. Apparently, the larger the lesion the greater the tendency to the former reaction.

As for Dr. McCouch's first comment, Dr. Shenkin has already properly put me in my place by showing that there is much more to be said in this field than I have mentioned.

DR. TEMPLE FAY: When Dr. Gammon asked me to discuss this difficult and complex problem, I am sure he meant me to do so from the clinical aspect. What I have to say, therefore, must be mediated in terms of clinical experience. Such an interpretation is limited by those conventional standards to which one has become accustomed, and yet which during the past few years have left one in great confusion with respect to the teachings of the past.

To me the "sign of Babinski," if it is, as Dr. Tower has brought out, a characteristic and persistent sign of section of the pyramidal tract, may offer an important clue to the motor systems from another angle. The sign has been considered by many as more or less a pathologic response, but it is a perfectly normal one in the baby. If one analyzes the movement in terms of segmentation (cortical, as against the lower motor level), and if one interprets Dr. Tower's section of this selective pyramidal system as equivalent to destruction of a motor system which is a comparatively recent addition phylogenetically, then one may see an analogy in the developing responses of the infant. During the early months of life, the free range of paddle movements and defense responses are compatible with the "sign of Babinski," but with control asserted by the development and myelination of the pyramidal tract, the Babinski sign is modified and suppressed, never to appear again unless the pyramidal influence is removed as a result of injury or disease.

I think there is plenty of evolutionary evidence pointing to a mechanism that has been developed out of a free-swimming state and that perhaps the greatest event in the life of the human species is the day of birth, when the infant arrives out of the water stage and becomes a land-breathing animal.

If the big toe is partially rotated outward and away from the digits, as is seen in the frog or the chimpanzee, the movement which is called the Babinski reflex will be seen to be really a fanning or paddle movement of a fin at the fish or amphibian level. When the baby grows up, he loses the Babinski sign, but later, if the pyramidal system is injured, the primitive motor patterns are released and the Babinski sign reappears. Coghill's analysis of movements in Amblystoma probably fortifies what Dr. Tower has demonstrated tonight. He found that the pyramidal system in Amblystoma developed after the appearance of the tail, head and eye movements. When the appendages appeared, particularly the digits, there was noted the formation of a "new motor system," with fibers that appeared after the original simple segmental pattern had already become established.

Coghill expressed the belief that as more selective movements appeared, an additional motor system developed to meet this need. If one will look at the over-all picture, and view the motor cortex as the site of integrated skilled movements developed for a purpose—all movement had at some time a purposeful meaning—one may get a different concept of the results of destruction at certain levels (i. e., how does the result manifest itself in terms of recent motor pattern controls over primitive reflex patterns and simple swimming movements?).

For instance, animals are tested in various positions—on the back, on the side or sitting—and residual motor responses are analyzed after selective operations. All are familiar with the influence of posture and the Magnus and de Kleijn phenomena. It seems to me that the animal should be placed in the "amphibian position" (on the belly, with the appendages extended to the sides and the thumbs and toes turned toward the head) and immersed in water, if possible, to nullify postural and antigravity effects, as well as to study the effect of operation on the original simple, free-swimming movements at the amphibian level.

I have found that the purposeless, jerking and twisting movements noted in animals during an induced convulsion are converted into an excellent pattern of free-swimming movements when the animal is suspended in water during the attack, with the belly down and the extremities free to assume the amphibian position and paddle function.

I should like to ask Dr. Tower whether she noted any difference after section of the pyramidal fibers between the rotary movements—call them "purposeless" if you like—such as

one can see in cases of acute chorea or of athetosis (extrapyramidal in a clinical sense) and those movements which are of prime flexor-extensor type, such as one sees in a major convulsive seizure.

It seems to me there is evidence of a definite clinical differentiation. Each type of movement is capable of an excitatory mechanism; each is characteristic and at times is free from the other component. Does the pyramidal system, of which 50 per cent of the fibers are of unknown nature, mediate both these phenomena? Or can one say that there is in the pyramidal system per se the better crystallization and objectifying of these rotary movements, of more recent phylogenetic acquisition, into a flexor-extensor pattern of primitive type, with the check modification that she spoke of?

In other words, is function of the pyramidal system divisible into two possible components; control of rotary movements and control of the flexor-extensor system?

I have enjoyed this presentation a great deal, and I am going back to the clinical work at hand with a new interest in Dr. Tower's interpretation of the function of the pyramidal tract.

Dr. Sarah S. Tower, Baltimore: In my work on epileptiform convulsions after section of the pyramidal system I have never seen anything that suggested, or in any way touched on, a choreiform type. But I have seen many reminders of the athetoid type. With my small experience in clinical neurology, I am cautious about getting into this field.

The suggestion that the Babinski response is a swimming derivative is extraordinarily interesting. There has been much speculation about the meaning of the Babinski sign—whether or not it is a primitive reaction. It is my impression that all such extrapyramidal responses come from primitive patterns which are anciently organized in the brain stem. The suggestion that the Babinski sign is part of a swimming mechanism is in this vein.

Dr. B. J. Alpers: Have any of the animals shown edema?

Dr. Sarah S. Tower: No, I have never seen it, although I have looked for it.

Dr. F. H. Lewey: Dr. Tower stated that the pyramidal tracts reenforce the segmental reflexes. In other words, loss of impulses over the pyramidal tracts should decrease the segmental reflexes. This, of course, is contrary to what one has learned previously. It used to be taught that the higher motor centers braked the subordinated motor levels and that the segmental reflexes were most exaggerated when freed from any regulation by higher centers. Probably this is one of the errors which one must rectify now.

What motor function survives when the whole cortex is out of commission except for the anterior central convolution?

What is known about the integration of pyramidal and extrapyramidal function in the final movement?

Dr. Sarah S. Tower, Baltimore. I would remind you of the effect of ordinary hemiplegia on the superficial reflexes, the abdominal and cremasteric reflexes, which are dereenforced, if one may say so. With a pyramidal lesion, the abdominal reflex disappears in all primates. In the monkey the cremasteric reflex also disappears. None of my chimpanzees were males, so I know this only for the monkey.

In ordinary hemiplegia in man, loss of pyramidal reenforcement of the segmental reflexes appears only in those which do not involve the antigravity mechanism. This mechanism is under release because of the associated extrapyramidal lesion, which Dr. Hines worked on extensively, in consequence of which these reflexes are exaggerated or spastic. But the abdominal and cremasteric reflexes are not of this nature and show the pyramidal depression, not the extrapyramidal release.

I believe that the final integration takes place in the internuncial and final motor mechanism of the cord. That, at least, would represent the final level of integration. In a normally functioning animal or human being there is, I presume, a tremendous amount of initial integration in the complex organization of the cerebral cortex, but that has not come under my survey at all in these experiments. Bard, in his cats with remnants of the frontal pole, tried to approximate a preparation in which a portion of the cortex exerts control over the pyramidal tract alone, but actually one cannot even approximate it because the field which gives origin to the pyramidal system also gives rise to numerous extrapyramidal systems. Moreover, for practical purposes, the extrapyramidal systems must be defined as including the prespinal collaterals of the pyramidal system because one cannot at present separate, for example, a corticonigral collateral of a pyramidal tract fiber from an independent corticonigral fiber. Until that can be done, all must be lumped together. Hence one could not possibly have a portion of the cortex controlling the pyramidal system, with the extrapyramidal systems thrown out.

Dr. G. P. McCouch: In support of Dr. Tower's contention—not that it needs support—that there is a tonic reenforcement of the central excitatory state from the pyramidal system, the following observation appears pertinent: If one excises area 4, allows the animal to recover

from the immediate effects of the operation and then transects the cord, there is an earlier recovery of reflexes on the side of the previous deprivation, the previously paretic side, than on the previously intact side, which suffered its entire spinal shock at the second stage. I realize that such an experiment is open to the criticism that area 4 contains extrapyramidal, as well as pyramidal, elements. I should be interested to see such an experiment repeated with section of the pyramidal tract rather than with ablation of area 4.

DR. MICHAEL SCOTT: I should like to ask Dr. Tower whether there is any clinical similarity between section of the pyramid as she made it and section of the pyramidal tract in the high cervical region.

DR. SARAH S. TOWER, Baltimore: All my animals with experimental sections in the cord have had at least some of the elements of spasticity, which is not true of those with section of the pyramid. A student of Dr. Hines, working on that problem, was able, by careful section of the cord, to get some preparations in which the spasticity was much more pronounced than in others.

As the pyramidal tract passes through the decussation and into the cord, it mingles with the lateral reticulospinal tract, overlaps the rubrospinal tract and plunges into the general proprius field of the spinal cord itself. Lesions of the cord are, therefore, inevitably mixed, and I presume the element of spasticity enters with this mixture. It is the chief difference between the results of section at the two levels.

Loss of discrete movement is, of course, characteristic of all lesions of the pyramidal tract, regardless of level. This is the common feature.

PHILADELPHIA PSYCHIATRIC SOCIETY

ARTHUR P. NOYES, M.D., *in the Chair*

Regular Meeting, Nov. 13, 1942

Symposium: Complications of and Contraindications to Electric Shock Therapy.

DR. THEODORE L. DEHNE: In the past two years my associates and I have treated about 120 patients at Friends Hospital. These patients represent a wide field of mental illnesses, many of which were treated semiexperimentally. In brief, we have come to the conclusion that electric shock therapy is most useful with agitated depressions, fairly useful with simple depressions and rather disappointing with manic reactions. A number of schizophrenic patients were given this therapy as a palliative rather than as a curative measure. Nearly all such patients became quieter and were more easily cared for. Early in our experience we hesitated to treat physically impaired patients, for a variety of reasons; as time passed, however, we concluded that many patients who exhibited what we believed to be disabilities contraindicating the induction of convulsions deserved such treatment because of the gravity of their mental illness.

Contraindications referable to the skeletal system included recent fractures and arthritic changes, particularly those of osteoarthritic type. However, several patients with severe arthritis were treated without damage. Of 120 patients, however, 5 suffered compression fractures in the thoracic region and 1 a fractured humerus, only the latter being considered serious.

Cardiac contraindications usually included arteriosclerosis, hypertension and cardiac enlargement due to any cause. However, several patients with advanced arteriosclerosis and 1 with pronounced enlargement of the heart with auricular fibrillation received the therapy without noticeable damage.

Pulmonary contraindications did not have to be considered in this series. Diseases of the central nervous system, particularly degenerative changes due to arteriosclerosis or senility, were considered contraindications, but patients with both types were treated with electric shock without apparent acceleration of damage to the central nervous system. One highly excited patient with dementia paralytica was given the therapy, after which he was somewhat quieter and easier to care for.

No deaths were directly attributed to electric shock. However, a highly excited alcohol addict with arteriosclerosis and organic heart disease had a stroke twenty-six hours after a treatment; he died subsequently.

In summary, we believe electric shock is a relatively safe procedure and that the reasons for its use should be dictated by the best results that may be accomplished.

DR. HOWARD K. PETRY, Harrisburg, Pa.: Electric shock treatments were first given at the Harrisburg State Hospital in February 1941. To date my colleagues and I have completed treatment in 148 cases.

Complications.—Skeletal System: Bilateral dislocation of the mandible occurred in 3 cases; pain and swelling of the right knee, in 3 cases; pain in the gastrocnemius muscle of the right leg, in 1 case, and pain in the back, in 6 cases.

Cardiovascular System: Vascular collapse, resulting in discontinuation of treatment, occurred in 1 case, and edema of the ankles due to cardiac decompensation, in 1 case.

Respiratory System: Prolonged apnea appeared in 3 cases.

Central Nervous System: An epileptiform convulsion, thirty-two days after the last treatment, occurred in 1 case; marked confusion, necessitating discontinuation of treatment, was present in 1 case, and manic excitement in a previously depressed patient, necessitating discontinuation of treatment, was noted in 1 case.

Muscular System: Ventral hernia and abdominal pain, with discontinuation of treatment, occurred in 1 case.

Miscellaneous Complications: Two conjunctival hemorrhages, both in the same case, were encountered.

No deaths occurred as a result of the treatment.

Contraindications were active or latent pulmonary tuberculosis, severe arthritis with deformity, poor cardiac tolerance to exercise and severe inanition.

The data on the results of therapy are analyzed in the following tabulation.

Psychosis	Total No. of Cases	Recovery	Improvement	No Improvement
Manic-depressive	43	25	12	6
Manic phase	6	2	1	3
Depressed phase	37	23	11	3
Involutional melancholia	34	19	5	10
Schizophrenia	60	7	12	41
Simple	12	1	4	7
Hebephrenic	3	..	2	1
Catatonic	20	3	4	13
Paranoid	25	3	5	17
Psychoneurosis	5	2	2	1
Unclassified	6	1	1	4
Total number	148	54	32	62
Percentage of cases	100	36.5	21.6	41.8

Average Duration of Illness

Psychosis	Recovery	Improvement	No Improvement
Manic-depressive	1 yr. 1½ mo.	4 yr. 3 mo.	9 yr. 10½ mo.
Involutional melancholia	1 yr. 3 mo.	2 yr.	2 yr. 10 mo.
Psychoneurosis	4 mo.	6 yr.	5 mo.
Schizophrenia	5.5 mo.	2 yr. 8 mo.	3 yr. 10 mo.
Unclassified	2.6 yr.	1.5 yr.	8.7 yr.

Average Age

Psychosis	Recovery	Improvement	No Improvement
Manic-depressive	44.2 yr.	50.7 yr.	43.6 yr.
Involutional melancholia	55 yr.	53.2 yr.	55.7 yr.
Psychoneurosis	34.5 yr.	36.5 yr.	33 yr.
Schizophrenia	27 yr.	30.6 yr.	30.9 yr.
Unclassified	47 yr.	51 yr.	46 yr.

DR. ARTHUR LINDENFELD, Allentown, Pa. (by invitation): Electric shock treatment was carried out at the Allentown State Hospital in 55 cases, representing various psychiatric diagnoses. In all cases roentgenographic and electrocardiographic studies were made before, at times during and at the conclusion of treatment. The following complications and contraindications were observed:

Skeletal System.—Advanced arthritic changes of the spine were noted in 2 cases. There were no fractures or dislocations.

Cardiovascular System.—In 2 cases treatment was refused, in 1 of which coronary disease, and in the other chronic rheumatic valvular heart disease with fibrillation, was present. In 2 cases treatment was discontinued, in 1 of which auricular flutter, and in the other persistent hypertension, with a blood pressure of 200 systolic and 120 diastolic, and peripheral sclerosis.

developed. In 1 case fibrillation was treated successfully. In 1 case with coupling and in another with auricular premature contractions therapy is being carried out, without complications thus far.

Respiratory System.—Treatment was refused in a case in which questionable tuberculous activity was present.

Central Nervous System.—In 1 case therapy was refused because of a history of convulsions earlier in life and electroencephalographic evidence of epilepsy.

No deaths occurred which were directly attributable to electric shock therapy. In 2 cases the patients committed suicide after treatment was discontinued, before they had shown satisfactory improvement.

DR. GRANVILLE L. JONES, Marlboro, N. J. (by invitation): At the New Jersey State Hospital, since Feb. 16, 1941, my associates and I have given electric shock treatments in a total of 508 cases. We have employed electric shock alone, electric shock combined with insulin, electric shock combined with curare and electric shock combined with insulin and curare.

We have no fixed contraindications. We consider each case on its merits, balancing the probability of improvement against the type or severity of the possible complications.

We had 16 cases of dislocation of the jaw and 1 case of subacromial bursitis. These complications were trivial. We had 1 case of subluxation of a cervical vertebra, with no serious results. We discovered 9 compression fractures of the thoracic vertebrae, resulting in nothing more than slight kyphosis. We take roentgenograms of the spines of all candidates, and any with pathologic conditions which reduce the flexibility of the spine or the density of the bone, such as severe hypertrophic or atrophic changes or previous injury or disease, are not considered suitable for treatment. We have sometimes used curare with such patients, as well as with a few who had suffered fractures during treatment. A patient aged 50 who had been psychotic for thirty-six years had a fracture of the humerus. Our results are in accordance with the observation of Graves and Pignataro that the incidence of fracture during metrazol shock depends more on the duration of the psychosis than on the age of the patient.

We had 1 case of pulmonary edema and 6 cases of circulatory collapse, the latter being probably of central origin. The symptoms were imperceptible pulse, apnea or respiratory distress and deepening cyanosis, changing to pallor. I know of no way in which to predict such a reaction; hence I am not certain that the cardiovascular contraindications have any bearing on it. We do not treat patients with past or present cardiac decompensation or disease of the coronary arteries or with arrhythmia that is demonstrably a symptom of organic disease. We have induced electric shock in patients with moderate arteriosclerosis, with moderate hypertension and with old rheumatic heart disease, and in the case of a patient with thrombophlebitis we combined electric shock therapy with curare. When tachycardia or arrhythmia appears, treatment is promptly discontinued. We do not take electrocardiograms except in doubtful cases or when symptoms arise.

Aside from disturbances of memory, which are almost always transitory, our only complication referable to the central nervous system has been prolonged or delayed convulsions, with no serious sequelae. A contraindication is any localized organic disease of the brain. Generalized disease of the brain, such as senility, arteriosclerosis without focal signs or even dementia paralytica, is not considered a contraindication if there are urgent psychiatric indications, such as severe agitated depression or exhausting excitement. We have treated a patient with Huntington's chorea and a few children with postencephalitic behavior disorders.

We have had no cases of tuberculosis, pneumonia or pulmonary abscess as a result of electric shock therapy. A case of pulmonary embolism will be discussed in connection with deaths associated with the therapy. We usually regard active tuberculosis as a definite contraindication to any form of shock therapy, but we treated a patient who had an active lesion, without spread of the disease. Inactive tuberculosis is not a contraindication. In 2 cases an acute infection of the respiratory tract developed during treatment. We suspend therapy under such circumstances, as well as when fever develops from any cause. In all cases roentgenograms of the chest are made before treatment, and for cause during and after therapy.

Other diseases observed were parotitis, in 1 case, and disseminated lupus erythematosus, in 1 case.

In 3 cases death followed exhaustion from psychotic excitement one, two and three days respectively after a single electric shock. In these cases death was probably not even hastened by the shock therapy, which was a desperate effort to terminate the severe and ominous exhaustion. In 1 case death resulted from an intravenous injection of magnesium sulfate, given for the curarization effect. In another case death was from pulmonary embolism, apparently as a result of infectious phlebitis, which complicated bilateral otitis media one week after the last shock treatment. Electric shock is probably contraindicated in cases of chronic disease of the middle ear, certainly when there is active infection.

A woman aged 23, with a psychosis diagnosed as manic-depressive insanity, perplexed type, had the cutaneous symptoms of lupus erythematosus on admission, which was not recognized as the disseminated form. She was given ten insulin and six electric shock treatments. Pleurisy developed, and treatment was discontinued. The shocks may have played some part in her death, which, however, did not occur until two months after the last treatment.

DR. HERBERT HERSKOVITZ, Norristown, Pa.: Since April 1940 174 patients have received electric shock therapy at the Norristown State Hospital. Two had fracture of a midthoracic vertebra and 4 dislocation of the jaw. The latter was reduced with no difficulty. There were no deaths or cardiac, pulmonary or other complications, except for memory defect. This defect, which has not been stressed by the previous speakers, I find to be rather general and often prominent. Therefore, patients whose occupation requires intellectual ability are selected for treatment with caution.

Prior to treatment each patient receives a thorough physical examination; in addition to the usual studies of the blood and urine, roentgenograms of the chest and spine and an electrocardiogram are taken. Until recently a roentgenogram of the spine has been taken after treatment.

The criteria for and contraindications to treatment include heart disease of any type; arteriosclerosis, either cerebral or generalized; hypertension; previous cerebral vascular accidents; any acute disease of the respiratory tract; previous fractures which have not healed firmly, and hernia. Healed tuberculous lesions, unless extremely small, are considered a contraindication to treatment. As a rule, patients over 60 years of age are not treated by this method. When an exception is made, the patient is studied thoroughly and treatment proceeds with caution. Prior to each session the patient's temperature and blood pressure are taken, and if either is elevated treatment is withheld. Emaciation is not considered a contraindication.

It is believed that the conservatism used in selection of patients for treatment explains the low incidence of complications at this institution. As the previous speakers have indicated, the course of the illness frequently determines whether or not the patient shall receive treatment. Electric shock therapy is of value for depressive psychoses, particularly involutional melancholia, but is of little value for schizophrenia.

DR. JOHN H. TAYLOR JR, Trenton, N. J. (by invitation): Since October 1940 my associates and I have employed electric shock therapy in 1,133 cases, in 448 of which electric shock was combined with insulin. In the remaining 685 cases electric shock therapy was used alone.

Complications.—These included loosening of teeth, in 22 cases; dislocation of the jaw, in 12 cases; dislocation of the shoulder, in 4 cases; fracture of the neck of the humerus, in 2 cases, and fracture of the head of both humeri, in 1 case.

There were 6 cases of compressed fracture in the thoracic region, with slight lateral displacement in 1 case. The fourth, fifth, sixth, seventh and eleventh vertebrae were involved in 1 case each, and the fifth and sixth vertebrae, in 1 case. In none of these cases were any neurologic symptoms evident, nor was any treatment other than supportive strapping employed; there apparently were no after-effects. Transverse fracture of the neck of the femur occurred in 3 cases.

We did not note any cardiac or pulmonary complications other than the expected reactions during treatment, or any complication referable to the central nervous system.

In several cases periods of forgetfulness and confusion developed, which lasted from two or three days to six months, the longer period being exceptional. The confusion, however, cleared up in all cases, and to date we have not noted any permanent mental impairment.

Types of Psychoses Treated.—We treated all types of functional psychoses, as well as epilepsy and psychosis with syphilitic meningoencephalitis. When we first began to use electric shock therapy, we treated manic-depressive psychosis, involutional psychosis and catatonic schizophrenia by this method alone. We found that the patients made spectacular improvement but that the improvement was not sustained. We now do not use electric shock therapy alone with any acute functional psychosis, but combine it with insulin shock. The combination of the two treatments has given more frequent and better sustained improvement than either treatment alone. We now use electric shock for patients with chronic disturbances or epilepsy and for disturbed patients with dementia paralytica. However, we emphasize that in our experience insulin therapy is the treatment of choice, and in the management of schizophrenia we use electric shock only as an adjuvant when the patient does not respond to insulin shock alone.

With the acute manic-depressive states, catatonia and involutional psychosis of the depressed, agitated type, we frequently start the insulin and the electric shock therapy simultaneously but continue the insulin shock treatment after the completion of a course of fifteen convulsions.

We have treated 22 patients with psychoses accompanying syphilitic meningoencephalitis who were admitted to the hospital in an excited and disturbed state. These patients all responded rapidly and within a few days made a good hospital adjustment. They were then given fever therapy.

Epilepsy: The Trenton State Hospital does not treat epileptic patients, as New Jersey has an epileptic colony at Skillman. However, a few patients who were subject to violent furors and showed homicidal tendencies are in residence at the Trenton State Hospital, for custodial reasons. Six patients were given a course of fifteen convulsions induced by electric shock, after which therapy was continued with one or two treatments a week for an indefinite period. These patients all showed improvement in their hospital adjustment; the frequency of their convulsions was diminished, and the periods of excitement entirely disappeared in most cases.

One case is interesting. A white man aged 42, who had been subject to epileptic seizures for thirty years, was admitted to the hospital in 1938; he was subject to seizures approximately every other day until Sept. 2, 1941, when he had 5 seizures. On September 3 he had 5 seizures; on September 4, 2 seizures; on September 5, 8 seizures; on September 6, 10 seizures; on September 7, 3 seizures; on September 8, 13 seizures; on September 9, 11 seizures; on September 10, 7 seizures, and on September 11, 12 seizures. On that date he was given his first electric shock treatment. The following day he had 10 seizures, and another electric shock treatment was given. On September 13 he had 1 seizure, and from that date until Jan. 11, 1942, a period of four months, he had no seizures. On January 11 he had a seizure, and another course of electric shock was started. He remained free from convulsions until Feb. 2, 1942; at this time, at his request, his family withdrew permission for treatment. Since that date he has continued to have convulsions approximately every other day, but there has been no return of his repeated convulsions.

Chronic Psychoses: By far the largest number of patients to receive electric shock therapy alone were the dirty, denuded, deteriorated and disturbed schizophrenic patients. These patients made a remarkable change in their institutional adjustment, and the majority improved to the point of remaining clothed, going to the cafeteria and working in occupational therapy groups in the wards. We found, however, that if the treatments were discontinued the patients soon returned to their previous level; therefore we maintain these patients on a regimen of one or two treatments a week for an indefinite period.

Curare.—We did not employ curare with our patients receiving electric shock therapy, but used it with 32 patients whom we treated with metrazol. We discontinued its use because in order to secure what we considered sufficient benefit from the drug, it was necessary to give large doses; in several instances respiratory paralysis developed, and artificial respiration had to be given for several hours.

Contraindications.—Our contraindications to treatment at present are cardiac decompensation, active pulmonary tuberculosis, hypertension, bony changes in the spine and hernias.

Dr. Thomas H. Wright Jr.: Four hundred patients at the Pennsylvania Hospital for Nervous and Mental Diseases were treated with electric shock. Curare was used routinely.

Skeletal System.—Dislocation of the left humerus occurred in 1 case. No contraindications referable to the skeleton were noted.

Cardiovascular System.—Complications were coronary thrombosis, in 1 case; auricular fibrillation, in 2 cases, and vasomotor collapse, in 2 cases.

A contraindication was severe cardiovascular disease.

Respiratory System.—Complications were severe apnea; rupture of a small pulmonary blood vessel, with recovery, in 1 case, and surgical shock, in a case of therapeutic pneumothorax.

A contraindication was severe active disease of the respiratory tract.

Central Nervous System.—A complication in 1 case was a generalized spastic state, which lasted for four days, with spontaneous recovery.

A contraindication was organic disease of the central nervous system.

Death occurred in 1 case, that of a man aged 50 years. A mild convulsion occurred during the first two minutes; breathing was satisfactory, then became irregular and stopped. The pulse continued to be good, but finally stopped. Permission for autopsy was refused.

Conclusion.—Contraindications center around severe organic illness. Even under such circumstances, however, the severity of the mental illness should be taken into consideration when one is trying to judge whether electric shock should be given.

Dr. C. A. Zeller: At the Philadelphia State Hospital 155 patients, the majority of whom had chronic schizophrenia, were treated. No fracture or orthopedic complication was noted. There were 12 dislocations of the jaw, 6 occurring in the same patient, in spite of prophylactic measures. A man of 48 presented split heart sounds, which returned to normal after suspension of treatment. A woman aged 55 died of bronchopneumonia two months after the completion

of several series of shocks, totaling sixty-two treatments (Alpers, B. J., and Hughes, J.: *J. Neuropath. & Exper. Neurol.* **1**:173 [April] 1942). Contraindications are an age of 60 or over, arteriosclerosis, hypertension, tuberculosis in any stage or location, cardiac disease of any type, any disease of bone and advanced inanition.

DISCUSSION ON PAPERS PRESENTED IN THE SYMPOSIUM ON ELECTRIC SHOCK THERAPY

DR. LAUREN H. SMITH: Electric shock therapy is proving effective in treatment of involutional melancholia and manic-depressive psychosis. At the Pennsylvania Hospital immediate recovery occurred in 70 per cent of patients with involutional melancholia, in 59 per cent of patients with manic-depressive psychosis, depressed phase, and in 56 per cent of patients with manic-depressive psychosis, manic phase. Manic patients did not maintain their recovery, and frequent relapse occurred. Electric shock therapy was not effective with schizophrenia, the rate of recovery not exceeding the rate of spontaneous recovery. Results in treatment of the psychoneuroses were likewise disappointing.

The complications arising in this type of therapy have been adequately covered in the various papers presented this evening These range from fractures and dislocations to complications involving the cardiovascular and respiratory systems, memory defects and even death. While from a statistical viewpoint these complications occur in only a small percentage of patients treated, they impose, nevertheless, the responsibility on the physician of considering with care the question of electric shock treatment.

Contraindications to electric shock therapy are a matter of opinion. Each patient should be considered individually, the advantages to be gained by possible psychiatric recovery always being balanced against the possible risks of the therapy.

DR. JOHN H. STAUFFER: At the Philadelphia General Hospital, my associates and I have so far treated 454 patients. One patient died, a man aged 70, who had graduadlly been growing worse for six years. He complained of loss of appetite and vague pains, became increasingly depressed and self accusatory, wanted to die and had to be fed with a tube. Physical examination showed mild electrocardiographic changes, due to arteriosclerosis. He was given four electric shock treatments combined with curare; during the fifth treatment he became dyspneic and died thirty-six hours later.

One man had fracture of the acetabulum, and another, aged 59, had abdominal hernia. A woman aged 47 had six successive convulsions after the first treatment. It was believed that she had had encephalitis a year prior to the treatment. There were several instances of hemorrhage of the conjunctiva and dislocation of the jaw and a few fractures of the vertebrae. One depressed patient with dementia paralytica, who had been treated with malaria with no improvement, was given electric shock therapy and is now back on the police force. We treated another patient with the same disease, who did not recover.

In certain cases we have induced subshock. One woman aged 72, with diabetes, made a good recovery under such treatment.

Shock apparently induces the malnourished patient to eat, and he gains in weight and strength.

In my opinion, if the patient's heart is in good condition it is safe to try electric shock therapy.

CORRECTION

In the article by Drs. Arnold M. Meirowsky and Feori F. Pipito entitled "Surgical History of Trigeminal Neuralgia," in the April issue (ARCH. NEUROL & PSYCHIAT. **49**:574, 1943), references to two articles by Drs. Grant and Weinberger were unintentionally overlooked. The new sentence beginning at the end of the seventh line of the last paragraph on page 579 should read: "Grant and Weinberger and Olivecrona[39] have already suggested . . . ," and reference 39 should read: "Grant, F. C., and Weinberger, L. M.: Experiences with Intramedullary Tractotomy: I. Relief of Facial Pain and Summary of Operative Results, *Arch. Surg.* **42**:681 (April) 1941; Experiences with Intramedullary Tractotomy: IV. Surgery of the Brain Stem and Its Operative Complications, *Surg., Gynec. & Obst.* **72**:747 (April) 1941. Olivecrona, H.: Tractotomy for Relief of Trigeminal Neuralgia, ARCH. NEUROL. & PSYCHIAT. **47**:544 (April) 1942."

Book Reviews

Autonomic Regulation. By Ernst Gellhorn. Price $5.50. Pp. 373, with index and bibliography. New York: Interscience Publishers, 1942.

The text is divided into five parts: (1) a general introduction; (2) autonomic reactions, involving primarily the respiratory and circulatory systems; (3) autonomic-endocrine integration; (4) autonomic-somatic integration, and (5) results and applications.

In his introduction, the author states that any understanding of the physiology of the mammalian organism must obviously take into consideration the mutual relationship of the various organs and determine how any change in the external environment affects the organs of the body. This consideration of the interrelationship of organ systems in environmental adjustment the author calls the "organismic principle." The central nervous system is involved in all these conditions.

The autonomic nervous system, by altering the circulation, respiration, heat production, heat loss, changes in blood volume and erythrocyte count, protects the cortex of the brain in a most effective manner from harmful alterations in the internal environment.

The author states that the book is an experimental survey in which he attempts to analyze the function of the organism under a variety of conditions. He states that under stress and strain there have been developed during the stages of phylogenetic evolution a set of reactions which retain the purposeful functions of the organism. The discovery of these principles becomes the task of an organismically oriented physiology; the application, the problem of a scientifically oriented medicine and psychology.

An attempt is made to understand the physiologic basis of the fact that it is the autonomic, and not the somatic, system that is responsible for the regulation of various adjustment reactions of body organs. It is pointed out that the autonomic nervous system differs fundamentally from the somatic centers inasmuch as changes in the internal environment which lead to a depression of the cerebrospinal system are accompanied by an increased excitability of the vegetative centers. These observations lead to a discussion of the mutual relation of the autonomic and the somatic nervous system. They show that the autonomic nervous system is not only an efferent system, carrying impulses from the somatic system to the various visceral organs, but an afferent system, the impulses of which significantly alter the excitability of the somatic system. This is illustrated not only for physiologic but for pathologic conditions, such as convulsions.

The autonomic reactions to hypercapnia, anoxia, asphyxia, hypoglycemia and hemorrhage are carefully considered and not only serve as examples of physiologic adjustment reactions, but throw important light on pathologic processes. An attempt is made to utilize these observations in the problems of neuropsychiatry. It is shown that the reactivity of the autonomic centers of schizophrenic patients is fundamentally different from that of normal persons. In the light of these observations, the physiologic effects of insulin, of hypoglycemia and of convulsions, induced either by drugs or by electric current, are studied, and a physiologic theory of the treatment of schizophrenia is presented.

Starting from a rather short consideration of the anatomic and physiologic foundations of the autonomic nervous system, the author proceeds carefully and methodically to expand his discussion, as already outlined, by a consideration of his own investigations and a review of the literature. His consideration of the literature is exhaustive, the bibliographic index listing 1,100 titles. One gets the feeling throughout that the author knows just what he is building, and as he fits fragments of evidence together, the shape of the structure becomes apparent.

Dr. Gellhorn states clearly that his mechanistic consideration of human reactions and emotions is not complete; whether or not one agrees with his attempt, it is apparent that his presentation of the problem is admirable. The point will eventually be reached at which all physicians will see that the consideration of psychic and somatovisceral factors in the production of human emotional responses is not a state in which the acceptance of one point of view demands a rejection of the other. It is perhaps merely a question of the emphasis on one or the other factor, both factors being constantly in action. This book may play a valuable part in guiding neuropsychiatrists toward such a point of view. This volume is recommended and should be a part of every one's neurophysiologic library.